

GUIDE FOR LIFE SCIENCE COMPANY DIRECTORS

First Edition



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ONE Rationale and link to *Code of Best Practice*

This *Guide for Life Science Company Directors* (the Guide) aims to support and enhance the performance of boards of directors leading public and private life science companies. It has been developed as a companion document to the *Code of Best Practice for Reporting by Life Science Companies (Ed 2, 2013)* (the Code). It outlines for less experienced directors or those new to life sciences issues typical to life science companies that are generally not typical in other industry sectors.

Innovative, technology-focussed companies in the life science industry have different pressures, such as unique regulatory requirements and a different business cycle than many other industries. Directors of

such companies therefore require additional, specialised knowledge that is not generally learned from available corporate governance materials or taught in mainstream governance courses.

AusBiotech has developed the Guide with the support of the Victorian Government and in collaboration with industry and governance experts. AusBiotech is committed to the development, growth and prosperity of the Australian biotechnology industry and developing the skills of leading executives is a key objective. An important component of a thriving life science industry is the quality of company governance, which in turn will support the broader industry.

This Guide is designed to:

- Promote best practice governance within the boards of life science companies and improve performance;
- Provide an informational source for people contemplating becoming a director on a life science company board, particularly less experienced directors, or those new to the life science sector; and
- Build on general governance guidance, by featuring the important aspects of life science that companies face.

TWO Scope of Guide

Rather than focussing on general governance considerations, this Guide addresses issues that may arise in life science companies, which would not be covered by mainstream governance materials, experiences or courses.

This Guide addresses a range of sector-specific issues that may be encountered in life science companies, whose activities may encompass bio-therapeutics, small molecule therapeutics, stem cell therapeutics, medical devices and diagnostics, agricultural applications, food technology and veterinary biosciences. However, the Guide has a strong emphasis on bio-therapeutics and small molecule therapeutics as this sector dominates the Australian industry at the time of publication.

Given the diversity that exists across the life science industry, the Guide refers to typical paths and scenarios rather than specific examples,

and does not cover the many deviations possible.

Given the global nature of biotechnology companies, users of this Guide are most likely to operate in multiple markets overseas. It is beyond the scope of this Guide to address individual country scenarios. Rather, the Guide provides insights into the Australian landscape, and the largest markets typically entered by Australian life science companies, the United States of America (US) and European markets.

The Guide should be considered in conjunction with its companion document, the Code, which provides a best practice framework and guidance on communication and disclosure.

The Code is intended to benefit all life science company directors and assist them to deal with the balance between confidentiality and continuous disclosure to investors.

2.1 Resources for all directors and would-be directors

The Australian Institute of Company Directors (AICD) conducts professional development programs and events and provides good practice information for directors and boards. The quality of these education resources – which are designed to positively influence governance practices – is widely recognised in Australian business circles and beyond. See www.companydirectors.com.au for more information.



THREE Best practice governance

Corporate governance responsibilities are common to all companies. The Corporations Act 2001 (Cth) requires that a company director or other officer exercise their powers and discharge their duties with care and diligence [section 180].¹ The Guide builds on, rather than replaces, good governance principles and highlights the areas where life science companies differ from other companies. However, the following takes a brief digression to cover the basic principles applicable to all companies.

The Australian Securities Exchange's (ASX) '*Corporate Governance Principles and Recommendations with 2010 Amendments*' (2010), quotes Justice Owen in the HIH Royal Commission and describes corporate governance as: "...the framework of rules, relationships, systems and processes within and by which authority is exercised and controlled in corporations. It encompasses the mechanisms by which companies, and those in control, are held to account."^{2a}

In August 2013 the ASX Corporate Governance Council issued a consultation paper seeking comments on a proposed third

edition of its *Corporate Governance Principles and Recommendations*. It has been revised and restructured to improve readability and to assist listed entities to comply with their governance disclosure obligations under the ASX Listing Rules. The third edition is likely to come into effect for an entity's first full financial year commencing on or after 1 July 2014. More details are available at www.asx.com.au

The ASX's guidance document articulates eight core principles that the ASX Corporate Governance Council believes underlie good corporate governance. These same basic principles also apply to unlisted companies.

Fundamental to any corporate governance structure is establishing the roles of senior executives and the board (Principle 1), with a balance of skills, experience and independence on the board appropriate to the nature and extent of company operations (Principle 2).

There is a basic need for integrity among those who can influence a company's strategy and financial performance, together with responsible and ethical decision-making which takes into account not

only legal obligations but also the interests of stakeholders (Principle 3).

Meeting the information needs of a modern investment community is also paramount in terms of accountability and attracting capital. Presenting a company's financial and non-financial position requires processes that safeguard, both internally and externally, the integrity of company reporting (Principle 4), and provide a timely and balanced overview of all material matters (Principle 5). The rights of company owners, that is shareholders, need to be clearly recognised and upheld (Principle 6).

Every business decision has an element of uncertainty and carries a degree of risk that must be managed through effective oversight and internal control (Principle 7). Rewards are also needed to attract the skills required to achieve the performance expected by shareholders (Principle 8).

Each Principle is of equal importance. Its practical implementation may vary as the company evolves and its circumstances change. It is therefore wise for a company to allow for a flexible constitution to enable the board to reform over the life cycle of the company.

STANDING AGENDAS

Also common to all companies is the typical agenda of standing items for board meetings:

Welcome, introductions and apologies
Minutes of previous meeting
Declaration of conflicts of interest
Actions arising from previous minutes
Progress report/s
Risk register update
Workplace health and safety report
Other business
Next meeting

3.1 Board responsibilities and monitoring performance

The board will be responsible for:

- Overseeing the company, including its control and accountability systems;
- Appointing and removing the chief executive officer, or equivalent;
- Where appropriate, ratifying the appointment and removing of senior executives;
- providing input into and final approval of management's development of corporate strategy and performance objectives;
- Reviewing and ratifying systems of risk management and internal control, codes of conduct, and legal compliance;
- Monitoring senior executives' performance and implementation of the strategy;
- Ensuring appropriate resources are available to senior executives;
- Approving and monitoring the progress of major capital expenditure,

capital management, and acquisitions and divestitures; and

- Approving and monitoring financial and other reporting.^{2b}

Performance is important to boards in two ways: Boards must monitor senior executives' performance; and individual board members must be accountable for their own performance.

It is recommended that a letter or agreement be issued when appointing a director or senior executive, to outline the expectations of the role. This may include the provision for review and evaluation of performance and may set out items such as performance indicators, particularly for senior executives. In smaller and non-listed companies, mechanisms and processes to outline and monitor performance may be less developed or formal, but are nonetheless just as important.

3.2 Selecting and inducting new directors

The biggest challenge for any company is appointing the right individuals to the board, to get the best mix. The composition of a board and the dynamics of its personalities are very important, but often not easily adjusted or changed. It is important to anticipate the dynamics in small start-up life science companies where there will often be tensions between the values of scientific research and the commercial and financial realities of identifying the most promising markets and making the best use of limited resources, which can prove damaging to a company's development.

For example, directors from a scientific research background and those from a commercialisation

background may have the same motivating factors (such as to find a better treatment for X), but will potentially choose, or be comfortable with, different paths to achieve the company's objective.

The directors will need to have a broad skill set to help the company in its pre-revenue phase as the board will need to be kept small due to the limitation on remuneration available to directors. On many start-up boards the directors do not get paid and this may limit the pool of director candidates.

Motivations to join a board in the life science industry may differ vastly, but many are driven by a common desire to find a cure, solution or a new and better way to improve and enhance people's lives. The life science sector at its core is about developing bioscience based technologies that transform into products and services to fuel, feed, protect and heal the population.

The motivation to remain a director on a life science company board is often about a genuine intent to see a technology developed to its maximum potential, in the knowledge that the medicine, test, device, functional food, stem cell treatment, biofuel or crop will have a positive impact on people's lives.

The ideal director in a life science company has an interest in the science, a considered appetite for risk, an understanding of the commercialisation process, marketing and business, and, in many cases, the patience and fortitude to work through pre-revenue phases. Some of the characteristics that may be desirable in a new board member are:

- Patience;
- Willingness to not be remunerated/rewarded for a considerable time;
- Specialist skill set;

- Available time to devote to the company;
- Understanding of the product development phase;
- Considered risk appetite;
- Ability to accept considerable and ongoing financial uncertainty;
- Past life science industry experience.

A new director ought to ask a number of questions to ensure appropriate knowledge of the company's activities and strategy, risk profile, etcetera. Key questions a director should consider are suggested in the AICD's Director Q&A on 'Evaluating an organisation before joining'³ Examples of some of these questions include:

- Who are the other directors? What are their skills and experience?
- Does the organisation know where it is headed? Are its aims achievable?
- Does the organisation have comprehensive risk management processes in place?
- What is the organisation's legal history?

3.3 Remuneration for directors

Remuneration can be a vexed topic. Any company will want to attract the best expertise possible to its board,

but how does a company do so at the start of life science company life cycle when there is often little to support the start-up activities, let alone to attractively remunerate directors?

One possibility is to offer equity or share options to attract the right people, and this option is used widely in the life science industry, in both pre and post-revenue companies. For example, the AusBiotech CEO Industry Position Survey of 2013 showed that 19.7% of responding companies used cash only to remunerate employees and directors, with 45.9% using options and 29.5% offering shares. Taxation issues need to be carefully considered when using equity incentives.

3.4 Conflicts of interest

Conflict of interest at the board level in the life sciences may arise given there is generally a smaller pool of appropriate board candidates to choose from with life science industry experience. It is therefore common for a board member with experience to sit on several life science company boards, and it is the responsibility of the individual and each board to determine any potential or actual conflict of interest exists.

Conflicts of interest (see glossary of terms for definition) are not necessarily a problem as long as they are disclosed and handled appropriately. For example:

- A director may choose to opt out of a discussion or decision if they believe themselves to be conflicted. In the case of a public company the director must absent themselves unless allowed to participate by the non-conflicted directors;
- A board may adopt a protocol whereby a director with a particular conflicting interest does not receive board papers relating to that field of activity;
- A board may appoint a sub-committee to oversee dealings between the company and a related party (for example, where the company regularly engages a consulting firm of which a director is also a principal);
- Declaration of conflict of interest (on a dedicated register) should be a standard and recurring item on every meeting agenda.

However, there may come a point where a director can no longer reconcile conflicting duties to two companies. At this point they will need to make a choice and resign from one of the boards.



FOUR Life cycles in life science companies

Life Sciences companies, like many companies have two distinct life cycles to consider: that of the company and that of its product/s on the 'road' to commercialisation. However, both of these cycles are atypical in life science companies and while they are addressed separately below, typically these may occur in parallel in a start-up biotechnology company.

4.1 Typical life cycle of a life science company

The life cycle of a life science company is not typical of many other industry companies. One of the key differences is the need for formal application to national regulatory bodies to gain approval to market in that country. To achieve successful approval, a comprehensive set of data on quality, safety and efficacy needs to be collated through a series of studies (in a predetermined format) over many years. Due to the length and expense of this process, many companies do not develop a product from conception through to marketing on their own. Instead they might develop the products to a certain point and then seek larger company partners or acquirers to complete this process.

Most large multinational life science companies are able to both develop products from in-house research to marketing and buy or in-license technologies, which can then be developed to market entry. As Australian biotech companies are relatively small in comparison with other companies in first world markets, they may plan to licence out or sell their technologies to others to develop.

Life science companies typically operate as a loss-making venture for a lengthy period. A start-up may not achieve revenue for many years. If it were to develop a product through to market it might not reach its marketing phase for ten to 15 years after its inception, whereas a company selling services or non-regulated product could generate revenue within weeks or months.

During the pre-revenue period, a life science company will be focussed on funding its research and development (R&D) program towards the eventual aim of either:

- Out-licensing the technology to a larger company for further development and marketing; or
- Pursuing the route to regulatory approval (and possibly pricing and reimbursement).

The role of investors is critical in the early stages, as is the board's role in attracting such patient (long-term) investment. During this time the company's value may rise or fall substantially, according to its ability to meet milestones in a timely fashion and achieve value inflection points along the development path. The company's value can also be enhanced through collaborative development pathways with other companies or partners; the receipt of grants, or news of a shortened/accelerated development pathway or interest expressed by a potential acquirer of the company's technology.

Independent of a company's own progress, market sentiment will be influenced by investors' perception of value.

Coupled with this atypical life cycle will be a need for different levels of expertise on the company's board at different times. While at the beginning of the life cycle scientific or product development expertise may be required, further down the track business development or sales/marketing expertise might be a priority. The composition of a board is therefore likely to need to change from time to time and as the company progresses through its life cycle.

Life cycle stages of a life science company



4.2 Gaining and retaining the balance: board composition over the life cycle of a company

Directors of a life science company need to ensure that the board is evolving so that the composition of the board is suited to the current stage of the company's life cycle, and that the board is also able to oversee the company's progress to the next stage. The board needs to find the right balance of executive directors (who have a management role in the company as well as their role as director) and non-executive directors (who are not in the company's management team, though they sometimes provide consulting services to the company in addition to their role as director). Within the category of 'non-executive directors' is a sub-category of 'independent' directors – non-executive directors who do not have a substantial service-providing role or a substantial shareholding

The ASX, while recommending that listed company boards have a majority of independent directors, also observe that *"all directors should bring an independent judgment to bear in decision making"*. While there are practical distinctions between independent and nonindependent directors, all directors must act in good faith in the best interests of the company. All directors are also obliged to exercise appropriate skills in the discharge of their duties.

A good independent director will bring a fresh, detached perspective to board deliberations, but all directors need to be able to consider the company's interests as a whole. It would therefore be unfortunate to be so caught up with a certain number of independent directors, that one ended up with unskilful, or non-contributing, directors.

START-UP OR SPIN-OUT

The start-up stage or spin-out from university research is often based on one innovative technology or platform. Once a technology with promise has been identified, and perhaps a prototype has been designed or a proof-of-concept trial conducted, the decision to commercialise it will mean the establishment of legal structures, such as registering a company and determining a governance structure (establishing a board). The company will often have established at least some IP assets, for example provisional patents.

The company should at this time be considering primary market research for its lead product or platform and beginning to formulate plans for regulatory approval, trials and pricing and reimbursement.

The board at this point typically consists of two or three people, including the founder or lead scientific researcher and primary investor.

PRODUCT DEVELOPMENT

This is the research and development (R&D) phase, which may include clinical or field trials. This is typically the highest risk period for the company as it has no revenue and large costs. The company may need to determine how to formulate and manufacture the technology into a product suitable for expanded proof-of-concept testing, and thereafter for toxicology studies. Once there is a sufficient basis to assume potential efficacy in humans, and with adequate toxicology study results to support first use in humans, a clinical trial program can be commenced.

This is a significant undertaking with formal regulatory format, assessment and hurdles and expertise in manufacturing, regulatory affairs, toxicology, pharmacology and drug development will be sought. This can be through in-house expertise or outsourced. Typically, smaller companies will outsource this type of specialised expertise. As companies

get closer to commercialisation the headcount can increase significantly.

The board during this phase continues its attention on monitoring the development of the technology against milestones and budget, but increases its focus on regulatory requirements, IP management, commercial considerations and the attraction of enough capital to fund development to the next stage. At this time thought may be given to appointing members of the board who are recognised in the investment and/or business community. If the company secures venture capital funding, the venture capital investor will usually nominate one or two directors to the board.

COMMERCIALISATION AND MARKETING

For some smaller companies, commercialisation means licensing or selling its technology to a larger company for further development. For others it is taking the technology to market itself. In both cases it is associated with injection of cash into the company either from upfront, milestone and royalty payments; or revenue streams, respectively.

In both cases, the milestone of achieving regulatory approval is pivotal. It either triggers payments through royalties to the innovator company, who licenced it out to the commercialising company, or it triggers the approval to market and hence the beginning of revenues to the commercialising company. Pricing and reimbursement might also need to be secured before product launch and marketing occurs. The key examples in Australia are listing on the Pharmaceutical Benefits Scheme (PBS) or Medical Benefits Scheme (MBS).

A company may also decide to enter the global market, which means seeking regulatory approval in other countries, so as to be able to access and export to those markets. Note

that Australian companies will at times initially apply for regulatory approval outside Australia first, due to the relatively small size of the Australian market compared with other markets. A typical example is a biopharmaceutical developer applying to the US Food and Drug Administration (FDA) for commencement of clinical. An FDA approval is often recognised by smaller markets which speeds access to the global market. At the point of product launch it is also the point at which manufacturing will need to meet market supply needs.

At this stage, the life science company builds sales and marketing expertise, employs or contracts a sales force. Supply chain logistics are also developed and/or improved.

Once a company has a product in the market, the board will focus on commercial outcomes, and may seek to appoint increased strategic marketing expertise onto the board.

The board will at this point ideally have reached optimal size (seven people, give or take two), with a broad range of skills, experience and business expertise, weighted toward the company's immediate needs and strategic next steps.

BUILD OR SPIN-OUT

Upon reaching the market, a company continues to support its product or platform generally for the life of its patent. The company is able to accelerate the development of and build the company's portfolio of earlier stage technologies or product line extensions, expanded indications, etcetera. It may, during this phase, choose to strategically set up a subsidiary company to specialise in a technology or group of technologies and work with an alternative lead target.

The board may benefit from increased skills in business development and marketing to build the balance sheet.

Any board needs to comprise people who have a certain skill set that can help a company to thrive. This is certainly the case for life science companies. While the hiring of consultants with specialist expertise may be considered, the typical life science company often does not have the financial means to engage external consultants, and must therefore rely on board members to provide advice and assistance. It is therefore vital that the right mix of board members is considered for different phases of the company life cycle. The most important thing to remember is to appoint wisely and make every board appointment count. It is easy to appoint directors and very difficult to remove them. Noting that a board member may have to perform more than one function or have more than one body of expertise, the suggested board composition may look as follows:

Point in life cycle	Size of board	Desirable skills and experience to consider include: (Note some skills may be outsourced.)
Start-up	Two or three people	A chief executive officer; Scientific research expert/s (often the founder or co-founders); Appropriately experienced business person; Investor(s); Finance or accounting expertise; Legal (IP and governance) expertise.
Product development	Three to four people	A chief executive officer; Scientific research experts (often the founder or co-founders); Investors; Business expert; Finance or accounting expertise; Legal (IP and governance); Regulatory expertise.
Commercialisation & marketing	Seven people, give or take two	A chief executive officer; Scientific experts; Investors; Business experts with marketing expertise; Legal (IP and governance); Finance or accounting expertise; Regulatory and clinical trial development expertise.
Build or spin-out	Seven people (full size), give or take two	A chief executive officer; Business experts; Sales and marketing expert; Legal (IP and governance); Business development; Finance or accounting expertise; Investors; Regulatory and scientific expertise; If considering a trade sale, advice from an investment banker.

4.3 Commercialisation pathways

TYPICAL DEVELOPMENT PATHWAY TO COMMERCIALISATION

Life science companies have many components that are common to one another and unique from other sectors when developing products, but the sector also spans a diverse range of typical pathways. The following gives a schematic showing a general and typical development pathway – typical across the life sciences.

See the appendices of this document for schematics showing typical development pathway, more specific to: (Appendix 1) A bio-pharmaceutical; (Appendix 2) a medical device; and (Appendix 3) a genetically modified crop.

range from a market research group, to a scientific advisory board, to a regulatory expert.

Noting that there is no direct marketing of certain pharmaceuticals to consumers allowed in Australia, it may be sensible to have a market research or advisory group of prescribers providing advice to the business.

4.4 Advisory groups or subject matter experts

Where a board has an expertise deficit, where there is a conflict of interest, or to show good governance, an advisory group or subject matter consultant may be used. This could

Development cycle typical to life science products

	0-2 years	2-4 years	4-6 years	6-8 years	8-10 years	10-12 years
Regulations	Patent Application	Trials Approval				Regulatory Approval
Trials	Basic Research/Proof of Concept	Early testing	Refinement and testing			
Product & Commercial Milestones				Prepare data package	Submit data package	Market Launch

FIVE Regulatory authorities and marketing approvals

5.1 Major regulatory authorities and typical pathways

Companies developing products in different markets are required to operate in accordance with the country's local regulations regarding the conduct of clinical trials, development and manufacture. The regulators consider the quality, safety and efficacy of the product they are asked to approve.

Regulatory authorities, their processes and their requirements for approval for marketing and sales will vary from product to product within life science sub-sectors, from sub-sector to sub-sector (for example, agricultural biotechnology versus medical devices), and from one country to another. However the path to obtaining regulatory approval for pharmaceuticals and medical devices is essentially the same in all major developed countries.

Human clinical trials are required to be performed under Good Clinical Practice (GCP) standards set by the International Conference on Harmonisation (ICH). Clinical trials that are not compliant with the GCP standards are invalid. See section 7.5 for more information on the ICH.

REGULATORY AUTHORITIES IN AUSTRALIA

In Australia, regulatory authorities include the following:

- Therapeutic products - the Therapeutic Goods Administration (TGA), www.tga.gov.au
- Gene technology and genetically modified organisms - the Office of the Gene Technology Regulator (OGTR) www.ogtr.gov.au
- Food safety (for genetically modified goods) - the Food Standards Australia New Zealand (FSANZ) www.foodstandards.gov.au
- Pesticides and Veterinary Medicines - the Australian Pesticides and Veterinary Medicines Authority (APVMA) www.apvma.gov.au
- Clinical trials conducted in Australia with unapproved therapeutic products are regulated by the TGA through the Clinical Trial Exemption (CTX) and Clinical Trial Notification (CTN) schemes, see www.tga.gov.au/industry/clinical-trials.htm

The major Australian regulatory authority is the TGA, which assesses and monitors activities to ensure that goods with therapeutic

claims available in Australia are of an acceptable standard. The aim of this is to ensure that the Australian community has access, within a reasonable time, to therapeutic advances and rapid scientific developments.

The TGA administers the *Therapeutic Goods Act 1989*. This legislation provides a framework for a risk management approach that allows the Australian community to have timely access to therapeutic goods which are consistently safe, effective and of high quality. Before being supplied in Australia, all products must be listed, registered or included in the Australian Register of Therapeutic Goods (ARTG) (see www.tga.gov.au/industry/artg.htm).

Other TGA responsibilities include regulating manufacturers of therapeutic goods to ensure they meet acceptable standards of manufacturing quality, monitoring products once they are on the market, and assessing the suitability of medicines and medical devices for export from Australia.

REGULATORY AUTHORITIES IN THE US

The FDA is responsible for protecting public health by assuring the safety,

efficacy and security of human and veterinary drugs, biological products, vaccines, medical devices, the nation's food supply including food additives, cosmetics, and products that emit radiation. Many Australian life science companies use the US regulatory path as the benchmark for their product development.

The FDA is also responsible for advancing public health by helping to speed innovations that make medicines more effective, safer and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Pathways in the US

Regulatory pathways differ from product to product. For the purposes of this Guide we focus on the most used regulatory path, that of the US (see www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm for more information). A typical pathway might be as follows.

How the FDA reviews medicines

To initiate human clinical development in the US, it is necessary to file an Investigational New Drug (IND) application with the FDA. The sponsor may choose to meet with the FDA at a pre-IND meeting to discuss the requirements for initiation of the first human study under this application. These early discussions are also used to discuss which regulatory path may be appropriate.

The equivalent filing for diagnostics is an Investigational Device Exemption (IDE).

Following lodgment of an IND application, the FDA has 30 calendar days in which to decide if a clinical hold is necessary (that is, if patients in the trial under the IND could be at an unacceptable risk). If the FDA does not raise any safety concerns that the sponsor would not be able to

address during the review process, on day 31 after submission of the IND the study may proceed. If a hold is imposed, the sponsor must address satisfactorily the issues raised by the FDA before the human clinical trial in the US can commence.

Prior to commencement of a trial, approval is required from the ethics committee of the institution conducting the clinical research.

At the end of Phase 2 of a clinical trial is one of the key meetings specified by the FDA. The primary focus of this meeting is to determine whether the company has adequate safety and efficacy data to proceed into Phase 3 clinical trial testing. This is also the time when the design and protocols for Phase 3 human studies are discussed with the FDA, and any additional information that may be required to support the submission of the New Drug Application (NDA) is identified.

The three major application types are: 505(b)(1) NDA, a 505 (b)(2) NDA or, an abbreviated NDA (ANDA). Other special regulatory provisions are discussed in the next section.

The FDA and the sponsor also finalise the requirements regarding the manufacturing processes and their control, and the methods and specifications for testing the quality of the materials and the finished product. A sponsor can request the FDA to review protocols regarding animal carcinogenicity studies, product stability and Phase 3 clinical trials under the Special Protocol Assessment⁴.

Regulatory inspections and approvals related to the manufacturing facilities for the product take place in parallel and in conjunction with the NDA review. A commercial scale manufacturing process (which adheres to cGMP, see section 6.3) is usually required to commence Phase 3 clinical trials (if not Phase 2) and changing the process afterwards can

add significant time and cost and potentially the need to repeat the clinical trial.

Upon successful completion of Phase 3 clinical trials, the sponsor meets with the FDA at the Pre-NDA meeting to discuss the presentation of data in support of the NDA. This meeting is conducted to uncover any major unresolved problems or issues with filing.

At the end of the review, the FDA can issue 'Not Approvable', 'Approvable' or 'Approval' letters. The 'Approvable' letter contains, for example, a list of correctable deficiencies and may also request commitments to do certain post-approval studies. The sponsor may request a meeting with the FDA to discuss these issues.

How the FDA reviews medical devices

A device's journey to market typically takes the following pathway:

An Investigational Device Exemption (IDE) allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a Premarket Approval (PMA) application or a Premarket Notification (510(k)) submission to the FDA. Clinical studies with devices that pose higher risk must be approved by both FDA and an Institutional Review Board (IRB) before the study can begin.

Premarket Notification (510(k)) is required when demonstrating substantial equivalence to a legally marketed device, when making significant modifications to a marketed device, and when a person required to register with FDA introduces a device for the first time. If a device requires the submission of a 510(k), it cannot be commercially distributed until the FDA authorises it. Examples of 510(k)s include x-ray machines, dialysis machines, fetal monitors, lithotripsy machines and muscle stimulators.

PMA refers to the scientific and regulatory review necessary to evaluate the safety and effectiveness of Class III devices or devices that were found not substantially equivalent to a Class I or II predicate through the 510(k) process. This is the most involved process. PMAs require valid scientific evidence that the probable benefits to health from the intended use of a device outweigh the probable risks, and that the device will significantly help a large portion of the target population. Examples of PMAs include digital mammography, minimally invasive and non-invasive glucose testing devices, implanted defibrillators and implantable middle ear devices.⁵

EUROPEAN MEDICINES AGENCY

The European Medicines Agency (EMA), formed in 1995, acts as the European Agency for the Evaluation of Medical Products (EMEA) to coordinate the evaluation of the safety, efficacy and quality of medicinal products within the EU. Unlike the FDA, the EMA is not a centralised body; rather it works to harmonise the existing national regulatory authorities throughout Europe by a process of mutual recognition and coordination. A key feature of the EMA is a procedure allowing a single application for marketing authorisation within the 27 member states through the Committee for Medicinal Products for Human Use (CHMP).

CHMP evaluates the application and provides a positive or negative recommendation. Certain therapeutic products can also be approved for marketing authorisation by single member states. Unlike the US, the EU is not a true single market. Pricing and reimbursement benefits can vary considerably between the EU states, consequently there are many instances where approved

drugs are not marketed in all member states. Clinical trial applications are not centralised in the EU, with submissions being made through respective national regulators, for example in the UK applications are made to its national regulator.

For more information see:
<http://www.ema.europa.eu/ema>

OTHER REGULATORY AUTHORITIES (SELECTED EXAMPLES):

- China – China Food and Drug Administration (CFDA) (formerly the SFDA)
- Japan – Ministry of Health, Labor and Welfare (MHLW)
- Germany – Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
- Netherlands – Medicines Evaluation Board (MEB)
- New Zealand – New Zealand Medicines and medical Devices Safety Authority (Medsafe)
- UK – Medicines and Healthcare Products Regulatory Agency (MHRA)

5.2 Orphan and other special designations

ORPHAN DRUG DESIGNATION

The TGA defines an orphan drug as a medicine, vaccine or in vivo diagnostic agent that is “*intended to treat, prevent or diagnose a rare disease; or is not commercially viable to supply to treat, prevent or diagnose another disease or condition*”. A full definition can be found in the *Therapeutic Goods Regulations 1990 (Section 16H)*.

Before an application to register an orphan drug on the ARTG, drugs need to first be designated as orphan drugs by the TGA. The quality, efficacy and safety of orphan drugs are assessed at the same standard as for other registered medicines.

In the US, orphan drug status by the FDA gives a manufacturer specific financial incentives and market exclusivity to develop and provide such medications. In addition, there are a number of other designations which are available to expedite review of therapies to treat life-threatening or seriously debilitating diseases, especially where no other satisfactory option exists, thus filling an unmet medical need in the marketplace.

In the EU, under Regulation (EC) No 141/2000, the EMA through the Committee for Orphan Medicinal Products (COMP) also grants a similar orphan designation scheme that attracts many benefits. Though the EMA grants market access to all member states, pricing and reimbursement are independently decided by each member state. Consequently an orphan medicinal product may not reach all European markets. Orphan designations with similar benefits apply in other countries, including Australia and Japan.

The orphan status attracts special benefits as summarised below, to encourage companies to develop products for rare medical conditions. They may be a very limited number of patients for whom the therapy would be useful. A period of guaranteed market exclusivity is one of the major benefits. A drug awarded an orphan designation is still required to meet the standard regulatory requirements and market approval processes.

	USA	Europe
Regulator:	FDA	EMA
Total patient population	<200,000	<5/10,000 ~ 250,000
Market exclusivity post approval (irrespective of patent status)	7 years	10 years
Accelerated review	Fast Track	Yes
Protocol assistance	Yes	Yes
Grants for orphan products	Yes	Yes
Tax benefits for trial expenses	50% credit on US trials	Country specific

BREAKTHROUGH THERAPY DESIGNATION

This designation requires preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. Fast track program features are implemented with additional and more intensive FDA guidance on an efficient drug development program.

FAST TRACK DESIGNATION

This designation may be granted on the basis of preclinical data. A sponsor of a drug that receives fast track designation will typically have more frequent interactions with FDA during drug development. In addition, products that have been designated as fast track can submit portions of a marketing application before submitting the complete application, known as 'rolling review'.

ACCELERATED APPROVAL

Accelerated approval can be used for speeding-up the development and approval of promising therapies that treat a serious or life-threatening condition and provide meaningful therapeutic benefit over currently available therapies. It is most often useful in settings in which the disease course is long and an extended period of time is required to measure

the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly.

Nevertheless, even after the drug enters the market, the sponsor may be required to conduct post-marketing trials to verify and describe the drug's clinical benefit. If further trials fail to verify the predicted clinical benefit, the FDA may withdraw approval.

A drug that has received a breakthrough therapy designation or a fast track designation can be eligible for the accelerated approval pathway, if the relevant criteria are met.

PRIORITY REVIEW

Under the *Prescription Drug User Fee Act 1992 (PDUFA)*, the FDA has a two-tiered system of review times. Priority review shortens the review goal date to six months from the Standard Review of ten months. This review designation is determined at the time of a Biologics License Application (BLA), NDA or efficacy supplement submission.

A drug that has received a fast track designation, breakthrough therapy designation, or those being evaluated for accelerated approval, can be granted priority review, if the relevant criteria are met.

5.3 Pathway for biologics

Whereas an NDA is used for drugs, a BLA is required for biological products.

In Australia, the TGA's *Biologics Regulatory Framework* regulates biologics separately from other therapeutic goods for a range of reasons including to minimise the risk of infectious disease transmission. Further details on biologics can be found in the TG Act *Part 3-2A-Biologics*.

In addition, refer to the TGA website at <http://www.tga.gov.au/industry/legislation.htm> for further information.

In the US, BLA's come under the jurisdiction of the US FDA's Center for Drug Evaluation and Research (CDER) division, which regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.

Biological products are regulated under the *Public Health Service (PHS) Act*, and are licensed under *section 351* of the PHS Act. The Act also provides for a system of controls over all aspects of the manufacturing process, and the authority to immediately suspend licenses in situations where a danger to public health exists.

Both the FDA's CDER and Center for Biologics Evaluation and Research (CBER) have regulatory responsibility for therapeutic biological products, including premarket review and oversight.

Following initial laboratory and animal testing that show that investigational use in humans is reasonably safe, biological products (like other drugs) can be studied in clinical trials in humans under an IND in accordance with the regulations. If the data generated by the studies

demonstrate that the product is safe and effective for its intended use, the data is submitted as part of a marketing application.

FDA approval to market a biologic is granted by issue of a biologics license, which is a determination that the product, manufacturing process and facilities, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product meet applicable requirements to ensure the continued safety, purity and potency of the product. Among other things, safety and purity assessments must consider the storage and testing of cell substrates that are often used to manufacture biologics. A potency assay is required due to the complexity and heterogeneity of biologics.⁶

5.4 Pathway for veterinary products

The regulatory framework for the registration of veterinary medicines and chemicals (pesticides) is administered in Australia by APVMA, which is responsible for ensuring the uniform regulation, control of manufacture, including quality assurance and compliance, and supply and sale of veterinary products. Companies holding registrations for veterinary products are also required to report annually to the APVMA in relation to their products ongoing safety and performance.

In general, if a company wishes to develop a veterinary product or active constituent and claim that it is capable of controlling a disease or provides some form of beneficial effect, then that product is required to be registered.

APVMA says: “If the product works as intended and the scientific data confirms that when used as directed on the product label it will have no harmful or unintended effects on people, animals, the environment or international trade, the APVMA will register the product.” Refer to the APVMA’s website at www.apvma.gov.au/about/index.php for further information.

The APVMA’s Manual of Requirements and Guidelines (MORAG) (see www.apvma.gov.au/registration/morag/rego_guide_vet.php) will greatly assist companies and their board when they are considering the development pathway for a veterinary product.

In the US, the FDA is the appropriate regulatory body for veterinary products. The equivalent filing to an IND for animal health applications is an Investigational New Animal Drug (INAD). In animal health the equivalent to an NDA and ANDA in FDA terms are New Animal Drug Application (NADA) for new drugs and Abbreviated New Animal Drug Application (ANADA) for generic products. Conditional Abbreviated New Animal Drug Application (CNADA) is equivalent to orphan drug status in human health.

The veterinary medicines section of the European Medicines Agency provides access to all information relating to veterinary medicines and their regulation for Europe. (See: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/veterinary_medicines_regulatory.jsp&mid=WC0b01ac058001ff8a)

5.5 Pathway for genetically modified (GM) crops

All fields trials (“limited and controlled releases”) and commercial release into the environment of GM crops must be licensed by the gene technology regulator (OGTR) under the *Gene Technology Act 2000*. The role of the regulator is to protect human health and safety and the environment by identifying and managing risks posed by the use of gene technology.

The *Gene Technology Act 2000* distinguishes between the approval pathway for field trials and that for commercial release into the environment, with a shorter process applicable to field trials. All applications require the preparation of a Risk Assessment and Risk Management Plan (RARMP). For further information, see: www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/factsheet_intentionalrelease-htm

SIX Manufacturing

The manufacture of life science-based products is regulated and requires manufacturers to adhere to quality benchmarks by having quality management systems in place. The most common for life science companies are discussed below. Life science companies should ensure they are compliant with the appropriate prevailing quality assurance and quality control guidelines.

6.1 Workplace health and safety

Australia has laws governing work health and safety and some states instead have their own laws. These laws require employers to eliminate risks to health and safety, so far as is reasonably practicable. If it is not reasonably practicable to eliminate risks to health and safety, the employer must minimise those risks so far as is reasonably practicable.

Employers have a duty to ensure, so far as reasonably practicable, the health and safety of both workers engaged by the employer, and of other people visiting the workplace.

Directors of life science companies need to understand their specific obligations as 'officers' under the work health and safety laws. Directors have a positive duty to exercise 'due diligence' to ensure that the company complies with its duties under the laws. This includes taking reasonable steps to ensure that the company uses and applies appropriate procedures, policies, training and health and safety practices.

Directors of life science companies carrying out clinical trials or manufacturing

must exercise due diligence to ensure that the employer complies with its specific duties under the work, health and safety laws in areas such as the handling and disposal of hazardous materials, and the use of radiation.

6.2 Good laboratory practice

Good Laboratory Practice (GLP) is the term used to describe quality systems that apply to the conduct of preclinical studies, typically safety and efficacy studies in animals.

The OECD provides principles of GLP to encourage "the generation of high quality and reliable test data related to the safety of industrial chemical substances and preparations in the framework of harmonising testing procedures for the Mutual Acceptance of Data (MAD)."⁷

6.3 Good manufacturing practice

Code of (or current) Good Manufacturing Practice (cGMP)* describes a set of principles and procedures that when followed help to ensure that therapeutic goods are of high quality. The basic principles of the guidelines are that:

- Each product cannot be tested, therefore samples are chosen from random batches for testing to indicate quality; and
- Quality procedures must be built into each batch of product during all stages of the manufacturing process.

There are different codes of GMP, depending on the type of goods. The TGA provide guidelines on: Good Manufacturing Practice for Medicines and Good Manufacturing Practice for Human Blood and Tissues. More information can be found at: www.tga.gov.au/industry/manuf-gmp-tg.htm.

6.4 Conformity assessment

A system known as *conformity assessment* is used to ensure that medical devices are of high quality. The classification of a medical device (into Class I, II or III) determines the conformity assessment procedures a manufacturer can choose to ensure that the device is adequately assessed. Higher classification devices must undergo more stringent conformity assessment procedures. More information can be found at: www.tga.gov.au/industry/manuf-devices-qm.htm#ca.

6.5 Chemistry, manufacturing and controls

Chemistry, Manufacturing and Controls (CMC) refers to the process of determining that the manufacture of medicines is under 'control'. The FDA provides various guidance for the manufacture of items ranging across the bio-therapeutic spectrum. See the following link for an example of those available from the FDA: www.fda.gov/drugs/industryinformation/guidances/ucm064979.htm.

* The 'c' in cGMP refers to 'code' in Australia, but refers to 'current' in the US.

SEVEN Typical phases of regulatory trials

7.1 Pharmaceutical clinical trials

Pharmaceutical clinical trials are the path a medicine travels from a concept, to testing in laboratory trials, to clinical trials, to reach the marketplace. This process takes place over many years and may average more than ten years. The typical product goes through a pre-clinical phase followed by four phases (shown below), each of which may include more than one trial. Clinical trials may also be used to identify the economic impact or cost – effectiveness of health outcomes, which may support the process of seeking pricing and reimbursement. In addition to the phases outlined below, the FDA has recently introduced a Phase 0, which is used to refer to exploratory, micro-dosing studies in humans. They are not required as part of testing a new medicine, but are part of an effort to speed up and streamline the process.

PRE-CLINICAL AND TOXICOLOGY STUDIES

Pre-clinical studies include pharmacology, pharmacodynamics, pharmacokinetic studies, as well as toxicology studies. Preclinical proof-of-concept is demonstration

of efficacy in an animal model of disease. Studies of the toxicology of a substance on animals and cells to prepare parameters for Phase I human subject clinical trials occur in the pre-clinical phase. They determine acute, subacute and chronic toxicity, carcinogenicity, mutagenicity, teratogenicity and effects on the reproductive system. See section on 'animal clinical trials' below.

PHASE 1 CLINICAL TRIALS TESTS A NEW DRUG OR TREATMENT IN A SMALL GROUP

The primary purpose of 'first in man' clinical trials in Phase 1 is to assess the initial safety and tolerability of the product in humans, typically in a short trial in a small number (20 – 100) of subjects. Phase 1 may include Phase 1a, with healthy volunteers, and Phase 1b in patients with a disease.

PHASE 2 EXPANDS THE CLINICAL TRIAL TO A LARGER GROUP OF PEOPLE

Phase 2 clinical trials establish the safe and effective doses of the drug, typically in the target patient populations, using sufficient patient numbers (100 – 300) and durations to provide reliable trends.

Phase 2a studies typically are smaller and shorter in duration than Phase 2b and evaluate different drug doses to see how they affect certain tests that can indicate whether the drug is working as expected. Phase 2b studies typically enrol more patients, are of longer duration and evaluate whether the drug is offering clinical benefits to patients. The main objective of Phase 2 is to define the dose, schedule and patient population for Phase 3 studies.⁸

PHASE 3 CLINICAL TRIALS EXPAND THE STUDY TO AN EVEN LARGER GROUP OF PEOPLE

The purpose of Phase 3 clinical trials is to test the safety and efficacy or otherwise of the new treatment in the target patient population. Such studies typically require larger numbers of patients (more than 300) and treatment duration that reflects the intended use of the drug. Drugs that are administered chronically generally require larger patient numbers and longer treatment periods to demonstrate a safety profile that is acceptable to regulatory authorities. Approval of a new drug generally requires completion of two successful Phase 3 clinical trials, with success measured by the drug showing a statistically significant benefit for the primary study end point.

PHASE 4 POST-MARKET AND COMMITMENT CLINICAL TRIALS

Phase 4 studies are required of or agreed to by a sponsor, and are conducted after the product has been approved for marketing. Regulatory bodies use post-market studies to gather additional information about a product's safety, efficacy or optimal use, or to determine alternative indications.

UNIVERSAL CLINICAL TRIAL TERMINOLOGY UNDER GOOD CLINICAL PRACTICE (ABRIDGED)

Sponsor: The organisation that initiates and funds the clinical trial.

Investigator: The clinician who conducts the trial. In a team setting there is a principal investigator. The investigator must be impartial, is not employed by the sponsor and has the responsibility to ensure that the trial complies with GCP.

Investigator's Brochure (IB): A collection of information prepared by the sponsor for the investigator. It includes information on the drug product including its physical, chemical and biological properties and information on the product's pharmacology.

Informed consent: Documentation to inform potential clinical trial subjects about the aims, methods, risks and benefits of the clinical trial, to provide a basis for voluntary enrolment.

Protocol: The document that presents the detailed guidelines for how the clinical trial is conducted. It will include the trial design, the number of subjects to be recruited, the end points to show the safety and efficacy of the drug, statistical methods for data analysis, the informed consent and confidentiality issues.

Case report form (CRF): The core document used to collect all data for each respective subject. The large amount of data must be complete and is independently cross-checked.

Inclusion and Exclusion Criteria: All clinical trials set out strict recruitment criteria that each subject must meet in order to be admitted to a clinical trial.

Monitoring: The strict process of interacting with clinical subjects and monitoring their well-being, the effects of the drug and placebo and recording adverse events and ensuring the accurate recording of this information in each respective CRF.

Adverse Event (AE): Any medical event that occurs in a clinical subject receiving either a drug or a placebo. This includes all events, whether or not they have resulted from the investigational drug.

7.2 Medical device clinical trials

The TGA advises that phases for a medical devices trial are determined by how invasive the device is⁹. For example, a device that is used externally will have different phases to an implantable device. While medical device clinical trials are not formally classified by phase, there are similarities between the stages of medical device development and medicine development.

The concept of a new device is often subject to extensive preclinical testing through bench testing, biomaterials testing, immunogenicity and carcinogenicity testing and, in appropriate instances, animal testing.

Initial clinical testing of devices usually involves a pilot study in small groups of patients. Any use of an unapproved medical device in humans, even in pilot studies, requires an exemption from the requirement for inclusion on the ARTG.

If the feasibility of the concept is proven, larger studies with well-designed protocols and a sound statistical basis are undertaken. Studies may be undertaken to confirm the performance and safety of changes in design or material of a device or to assess the device's performance against new clinical indications. The clinical safety and performance of many devices depends largely on the experience and training of the clinician using the device. These are important points for consideration in assessing a clinical trial application.

7.3 Field trials

Applications for field trials of crops with genetically modified plants must be submitted to and undergo evaluation from the appropriate authority of the respective country or state. The phases of development for a genetically modified crop can be divided into four stages (also see Appendix 3):

TECHNOLOGY DISCOVERY

The process begins with a research stage, where scientific principles or ideas are explored.

PROOF-OF-CONCEPT

The proof-of-concept phase is where a gene or genes are tested, usually in model plants, for those which show the most promise for application to crop plants.

FIELD TRIALS

Once the technology has reached the trial phase the modified genes are tested under field conditions experimentally to determine the likely success of the crop, and sometimes also the performance of elite varieties. Not all field trials are an indication of imminent commercial release; some are large scale experiments, rather than a step towards commercialisation.

COMMERCIALISATION

Commercialisation can commence once the successfully trialled traits have obtained regulatory approval. At this point seeds are bulked for sale and the business plan implementation may commence.¹⁰

Research commissioned by CropLife International indicates it takes on average 13 years of R&D and USD \$136 million to bring a new GM crop trait to market.¹¹

7.4 Animal trials and ethics

Animals are sometimes used in the testing of drugs, vaccines and other biologics as well as medical devices, mainly to determine the safety of the product. There are often difficult and challenging ethical judgements to be made regarding the use of animals for scientific purposes. For drugs and biologics, the focus of animal testing is on the drug's nature, chemistry and effects (pharmacology) and on its potential damage to the body (toxicology). Animal testing is used to measure:

- How much of a drug or biologic is absorbed into the blood;
- How a medical product is broken down chemically in the body;
- The toxicity of the product and its breakdown components (metabolites); and
- How quickly the product and its metabolites are excreted from the body.

For medical devices, the focus of animal testing is on the device's ability to function with living tissue without harming the tissue (biocompatibility). Most devices use materials such as stainless steel or ceramic that are known to be biocompatible with human tissues. In these cases, no animal testing is required. However, some devices with new materials require biocompatibility testing in animals, prior to being tested with human subjects.

All Australian organisations conducting research using animals must comply with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes 2004* and nominate an Animal Ethics Committee (AEC) to oversee the conduct of the organisation's ethical and humane care and use of animals for scientific purposes. The

Code for investigators, teachers and institutions using animals for research are designed to:

- Ensure that the use of animals is justified, taking into consideration the scientific or educational benefits and the potential effects on the welfare of the animals;
- Ensure that the welfare of animals is always considered;
- Promote the development and use of techniques that *replace* the use of animals in scientific and teaching activities;
- Minimise or *reduce* the number of animals used in projects; and
- *Refine* methods and procedures to avoid pain or distress in animals used in scientific and teaching activities.

7.5 Guidelines for clinical trials

The International Conference on Harmonisation (ICH) is a body that has its origin in the Declaration of Helsinki and defines international ethical and scientific quality standards, or GCP, for designing, conducting, recording and reporting clinical trials that involve human subjects. Specifically, it includes standards on how clinical trials should be conducted, the roles and responsibilities of clinical trial sponsors and clinical research investigators, and monitoring methodology. In the pharmaceutical industry, monitors are often called Clinical Research Associates (CRA).

Compliance with the ICH's GCP standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, and are used by governments to transpose into regulations. Compliance also ensures that there is a unified international standard to facilitate the

mutual acceptance of clinical data. The guideline was developed with consideration of the current good clinical practices of the EU, Japan, the US, Australia, Canada, the Nordic countries and the World Health Organization (WHO).

The ICH is a global collaboration initially formed between regulatory agencies and pharmaceutical industry associations from the US, Europe and Japan. Many other regulators, including the TGA conform to these standards. The GCP guidelines are primarily based upon two core documents: *FDA 21 CFR Parts 50, 56 and 312*; and the *ICH Harmonised Tripartite Guideline for Good Clinical Practice*, and provide a standardised language and approach to human clinical trials.

For further information, visit the website at www.ich.org/products/guidelines/efficacy.html.

7.6 Compassionate use and continued access provisions

An unapproved medicine or medical device may normally only be used on human subjects through an approved clinical study in which the subjects meet certain criteria, and

then only used in accordance with the approved protocol by a clinical investigator participating in the clinical trial. However, there may be circumstances under which a health care provider may wish to use an unapproved product to save the life of or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. Patients and physicians faced with these circumstances may have access to investigational products for a single patient or small group access under 'Compassionate Use' provisions.

Also, it is not always possible to discontinue patients from a trial, and companies may need to provide patients with treatment beyond clinical trials under 'Continued Access' provisions.

7.7 Governance issues arising from clinical trials

The regulation concerning clinical trials, particularly for medicines, has increased over the past 50 years, in part due to the thalidomide disaster. Informed consent provisions are highly important and are derived from internationally-accepted guidelines.

The conduct of clinical trials is not to be taken lightly and expert advice is recommended to ensure compliance with international and local guidelines, and to minimise liability issues for the company. Liability insurance needs to continue beyond the end of the clinical trial's completion.

A board should ensure there is adequate budgeting for any clinical trial (which usually cost upwards of \$1 million, even for a small trial) as it is unethical to stop a trial due to funding problems.

Regulatory trials also pose a number of issues in relation to reporting and communication. The success or failure of trial milestones may be material to the company and may require reporting to the investment community. Suggested guidelines for what should be reported in relation to regulatory clinical trials are outlined in the Code.

Given the importance of pricing and reimbursement, life science companies need to consider how the design of clinical trials may assist in the process of obtaining pricing and reimbursement (for example, by demonstrating greater cost effectiveness than existing therapies), as well as demonstrating safety and efficacy.

EIGHT Pricing and reimbursement

Consideration and research of the final pricing and prospects for pricing and reimbursement should be considered early in the development of a product and reviewed as clinical trials progress. This leads to the creation of the target product profile that shows the key characteristics required for a well-differentiated product, which will be profitable. Depending on the country in which a product is to be sold and the biotechnology sub-sector, opportunities for pricing and reimbursement (access to payers) will differ substantially and usually take the form of listing on a formulary or scheme.

Pricing and reimbursement will depend on the structure of the healthcare system. For example, medicines may be purchased by patients themselves, a health care organisation on behalf of patients (hospitals), by an insurance plan (public or private) or by governments. Public plans may be structured in a variety of ways, including:

- Universal, as in Australia's PBS;
- Restricted by age, as in the Ontario Drug Benefit Plan for seniors;
- Segmented by disease group, such as Manitoba's cystic fibrosis drug plan;

- Aimed at supporting specific employee types, such as Veterans' Affairs for US ex-military personnel;
- Geared to income, such as US Medicaid programs in many states; or
- Structured to respond to the 'catastrophic' impact of expenses incurred by those with serious diseases or high costs relative to income.

Evaluation for listing is often based on 'cost-effectiveness' according to the discipline of pharmacoeconomics. This specialised field of health economics looks at the cost/benefit of a product in terms of quality of life, alternative treatments (drug and non-drug) and cost reduction or avoidance in other parts of the health care system (for example, a drug may reduce the need for a surgical intervention, thereby saving money). Structures like the United Kingdom's National Institute for Health and Clinical Excellence and Canada's Common Drug Review evaluate products in this way. Some jurisdictions evaluate products via individual drug benefit plans, or hospitals may have their own review committees to advise which medicines to fund from a hospital's budget.¹²

8.1 Australian assessment of health technologies for reimbursement

The Australian Government's health technology assessment (HTA) agencies are the TGA, the Medical Services Advisory Committee (MSAC), Pharmaceutical Benefits Advisory Committee (PBAC) and the Prostheses List Advisory Committee (PLAC). These agencies have complex and inter-dependent relationships. Each entity has discrete functions and responds to different policy needs.¹³

The single entry point, known as the Health Technology Assessment Access Point (HTAAP), commenced operation in 2010 and assists potential applicants for HTA for reimbursement where the applicant is uncertain about the funding for which their technology may be eligible, or where their technology may need to be assessed by more than one expert advisory committee, such as in the case of co-dependent and hybrid technologies.¹⁴

PHARMACEUTICAL BENEFITS SCHEME (PBS)

In Australia, the majority of pharmaceuticals are reimbursed under the PBS, which is administered by Medicare Australia on the recommendation of PBAC. The PBS provides a list of marketed medicines that are subsidised by the Australian Government. Although some approved products are marketed without the subsidy in Australia, the PBS represents the major market for prescription medicines outside of hospitals, accounting for over 90% of prescriptions.

At times, post-marketing (Phase 4) clinical trials are conducted by sponsors seeking alternative reimbursement indications on the PBS.

MEDICAL BENEFITS SCHEDULE (MBS)

Reimbursement is available in Australia for medical procedures, including those involving medical devices and diagnostics, via the MBS, which is administered by Medicare Australia on the recommendations of MSAC.¹⁵

PROSTHESES LIST

Private health insurers are required to pay benefits for a range of prostheses that are provided as part of hospital treatment for which a patient has cover and for which an MBS benefit is payable for the associated professional

service. The PLAC reviews and recommends prostheses for listing.

The type of products on the prostheses list include cardiac pacemakers and defibrillators, cardiac stents, hip and knee replacements and intraocular lenses, as well as human tissues such as human heart valves, corneas, bones (part and whole) and muscle tissue.¹⁶

IN OTHER PARTS OF THE WORLD

Opportunities for pricing and reimbursement vary dramatically from country to country. The pricing and reimbursement system in the US, for example, is far more fragmented compared to Australia. It is based on a mixed public/private third-party payment system whereby government, employers and individuals share the cost of care. Premiums are paid to private insurance companies for private coverage either by individuals or employers. Government payments are provided at federal and state levels to statutorily defined populations (for example, elderly, poor, disabled and veterans). Many private insurers also cover Medicare and Medicaid populations financed by the government.¹⁷

Other players and intermediaries also exist in the payment systems such as 'preferred provider organisations', 'health management organisations' and 'managed care organisations'.

8.2 Pathways to pricing and reimbursement in Australia

PHARMACEUTICAL BENEFITS SCHEME

Listings are made on the recommendation of the Australian PBAC. Recommendations by PBAC are not binding and Ministerial approval (and in some cases Cabinet approval) is also required.

Further information on the ten step process can be found at: www.pbs.gov.au/info/industry/listing/listing-steps.

MEDICAL BENEFITS SCHEDULE AND PROSTHETICS

Applications for new items, or amendments to existing MBS items, may be submitted to MSAC for assessment.

Further information on the four stage process can be found at: www.msac.gov.au/internet/msac/publishing.nsf/Content/msac-application-process-lp-1.

NINE Financial management

9.1 Capital raising

A typical life science company needs a large amount of capital on an ongoing basis, usually for the dominant purpose of R&D, working capital or commercialisation¹⁸. Given that the majority of life science companies will have little or no revenue to support development and commercialisation, attracting investments and raising capital can therefore be difficult, and can take many forms. Fund raising success is driven by broader market economic conditions, as well as a company's progress along the commercialisation path of the product/ portfolio and the competitiveness of the technology in markets.

BioShares releases annual capital raising figures for the industry¹⁹, which underscore the volatility and uncertainty of the capital-raising environment:

2012	\$256.9 million
2011	\$630 million
2010	\$554 million
2009	\$672 million
2008	\$185 million

9.2 Sources of capital

Of the 54 companies that respond to the *AusBiotech 2013 Industry Position Survey*, 24 raised capital in 2012. An overwhelming 87.5% did

so by issuing equity, in the forms of equity issue, convertible notes or rights issue. However, there is a broad spectrum of sources of capital and capital raising strategies and Australian companies draw on a mix of external funding sources to support their business activities. These are not specific to life sciences, but nevertheless will be of great importance to life science companies.

ANGEL INVESTORS

Angel capital is provided by an individual using their own money. By definition, it is a high risk-reward personal asset class comprising investment (financial and intellectual) into business opportunities. Angel investors are individuals with an interest in entrepreneurship and growing innovative, new businesses. They are typically wealthy, well- connected and seasoned business people, entrepreneurs or professionals. The majority invest not just for financial gain, but for the personal satisfaction of helping innovative new businesses succeed. Angel investment is also sometimes referred to as seed capital.

Angel groups and syndicates are investors who work together to leverage their combined intellectual and financial capital. Pooling resources, expertise and money allows these groups to take on larger

investments and increase the level of support for entrepreneurs.²⁰

VENTURE CAPITAL

Venture capital (VC) is provided by an institution or fund that manages other people's money. VC funds in Australia have raised more than \$2 billion and invested \$1.5 billion in 250 companies in the last ten years.²¹

The venture capital fund makes money by owning equity in the companies it invests in, which usually have a novel technology or business model in high technology industries, such as biotechnology. Venture capital is a subset of private equity.²²

A venture capital fund will have a fixed term, such as ten years, in which to realise its investments (by, for example, selling its shares as part of a trade sale or on-market transaction) and distribute the net proceeds to investors.

DEBT CAPITAL RAISING

In addition to equity capital raisings, businesses are able to externally fund their operations through debt issues and/or business loans. In Australia, the funding of non-financial corporations are split around 50:50 between equity (listed and unlisted) and debt/loans.²³

Due to the nature of the assets in life sciences, which can be secured under debt facilities, director's assets may

be taken into account as collateral or consideration for business loans. Early-stage life sciences companies may find it difficult to borrow as cash is often the only asset of the company.

Companies may issue hybrid instruments such as convertible notes, and there are specialist providers of such funding. However the Board needs to take advice and weigh up the pros and cons of these instruments, such as the dilution of other shareholders where the notes are converted to equity.

INITIAL PUBLIC OFFERING (IPO)

Once a company has sufficiently matured and reached a minimum size, it may raise capital by issuing equity via an IPO. This is its first sale of shares or stock to the public and results in the company being publicly listed on an exchange. The cost of listing and compliance is substantial, and therefore this option may not be suitable until a company reaches a certain size, and has built a valuable base. Being publicly-listed means that a company's market valuation can be determined easily and this can impede some negotiations if the board's view of its assets value mismatches the market value of the company.

ISSUING EQUITY

Private equity and placements

Investing in a company in return for equity ownership is referred to as 'private equity' when the company is not publicly listed and a 'share' once the company is listed. A company that is publicly listed on an exchange may make a 'placement' of shares, which involves the issue of securities to a limited number of significant and/or predominately institutional investors. They can be made to a select group of existing shareholders or may be used to introduce a new cornerstone investor to the share register.

'Placements' provide the fastest mechanism to raise capital (one to two days) and are generally the least risky option to raise funds due to

the truncated issue timetable, which reduces exposure to market risks. They are also generally less costly to underwrite and require a smaller price discount relative to current market price.

However, placements have the greatest potential to result in dilution of existing (particularly retail) shareholders' economic and voting interests. For listed companies, placements are subject to a 15% (of issued capital) limit (or, for smaller listed companies, a 25% limit if pre-approved by shareholders) in a 12-month period. Any issues over that threshold, unless certain exceptions apply, can only be raised with shareholder approval. Placements are also governed by:

- Takeover laws, which restrict significant changes in ownership of a public company unless a full takeover offer is made; and
- Prospectus laws, which require that detailed information be provided to investors unless certain exemptions apply (e.g. small scale offers, offers to sophisticated investors).

Rights issue

A rights issue is an offer to all existing shareholders to subscribe for additional securities in the company in proportion to their holding, usually at a discount to the current market price of the shares. Shareholders have the choice of accepting the offer in whole or part.

Share purchase plans (SPP)

An SPP is an offer of securities up to a set dollar value to existing shareholders of a listed company.

While such an offer can be made to all shareholders, recent practice has often seen an SPP linked to an institutional placement. In this case, the offer is only made to those shareholders who were not offered shares through the placement.

Unlike a rights issue, a SPP is not a pro-rata offer, meaning that all

shareholders are not offered shares based on the size of their holdings. It is essentially a rudimentary means to provide an opportunity for retail shareholders to take up new shares, without actually providing equality of treatment. It should be noted that an SPP can dilute the value of equities for major shareholders.

Royalty monetisation

Royalty monetisation is the selling of rights to a royalty stream or a portion of a royalty stream in exchange for an up-front payment. There are a number of sophisticated investment firms who buy the rights to royalty streams in the life science and healthcare sectors. In some cases, licensees themselves may agree to convert a license with milestone payments and royalty payments to a fully paid-up license by paying the licensor a one-off amount. The immediate advantage of royalty monetisation is it provides immediate access to new working capital for product development and/or business operations. Such funding also has the benefit to the company of being non-dilutive to shareholders. As with any financing, companies need to carefully evaluate the cost of capital to access such funding against alternative forms of financing.

ISSUING NOTES AND BONDS

A *bond* is an instrument of indebtedness of the bond issuer to the holders. It is a debt security, under which the issuer owes the holders a debt and, depending on the terms of the bond, is obliged to pay them interest (the coupon) or to repay the principal at a later date, termed the maturity.

Interest is usually payable at fixed intervals (semiannual, annual or sometimes monthly). Very often the bond is negotiable, that is, the ownership of the instrument can be transferred in the secondary market. They are usually issued for at least ten years and for up to 30 years.

A short term bond (typically five years or less) is called a *note*. Bonds and notes are a hybrid security with debt and equity-like features.

A *convertible bond or note* means that the holder can convert into a specified number of shares in the issuing company. A convertible note can be recognised as a liability on the balance sheet so caution is needed to avoid balance sheet insolvency.

Certificates of deposit or short term commercial paper are considered to be money market instruments and not bonds. The main difference is in the length of the term of the instrument.

GRANTS AND INCENTIVES

Other common forms of raising capital include applying for Australian and/or state/territory government grants, as well as accessing the cash refundable component of the Australian Government's *R&D Tax Incentive*, which came into effect in July 2011. This is applicable to companies with turnover under \$20 million.

Grants are available from disease foundations, patient support groups, as well as organisations and governments in other countries, such as the US National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA) and the UK-based Wellcome Trust.

9.3 Motivations for investing in life science companies

Most investors in life science companies tolerate higher levels of risk, which is commensurate with that of investors in the mining industry, where risk is higher but when successful, returns too are higher than average. The motivations of investors in the life sciences come under four general categories:

- Seeking explosive capital growth, or returns greater than stock markets' index averages;
- Seeking to invest where there will also be a community benefit from the product/s in development (such as medicine or medical

technologies, or processes that increase crop yields);

- Appeal to investors looking to diversify or balance a portfolio; or
- Equities in this area are less impacted by broader economic conditions (uncorrelated) and therefore perform better in volatile markets.

Motivations will differ depending on the type of investor. For example, venture capitalists may seek capital growth while institutional investors may prefer to receive dividends. The types of investor a company attracts will change over time and depend on the company's point in the life cycle, driven by investors' needs.

9.4 Developing a preferred group of investors

A company cannot always choose investors, particularly in the earlier life cycle stages, however, when in position of choice a life science company will benefit from long-term and patient investors, ideally attracting people who bring knowledge along with capital and who have an appropriate risk appetite.

The most attractive investors are those that are willing to support a company for the long term (many years) and ensure sufficient resources for on-going development, which may mean follow-on funding. It is typical for an investor in the very early stages to be asked to make further investments into the same technology over time, to help bring that technology to its next inflection point (and/or to reach the point of earning revenue) and the depth of the capital pool is an important factor.

Many start-up companies look to family and friends for seed capital and while this is at times necessary, it can create a complex pool of investors with little but cash to offer.

Apart from providing much-needed capital, the ideal investor also brings

skills and relevant experience to the company to assist in its development and sparing the need for the company to pay for expert advice.

9.5 Cost of capital

The cost of attracting capital can be significant, especially in early stages when revenues are still years away. Typically funds are secured by issuing new equity in the company, rather than taking loans, potentially diluting the asset value of other shareholders if the total company value has not grown in proportion. The investor therefore takes a stake in the company and with it the risk the company will or will not be successful, in return for a portion of the company's equity.

Negotiations for how much equity to exchange in return for capital is an issue fraught with uncertainty. It is not uncommon for the cash needed to get to the next inflection point to be an order of magnitude higher than what was originally estimated.

9.6 Investor relations and the board's role

Companies are strongly encouraged to adopt best practice in reporting events to investors. High standards of communication and market disclosure promote investor confidence, an important factor in enhancing market liquidity and availability of capital for life science companies.

As well as these benefits, the discipline required of a publicly-listed company in gathering and analysing information to support the disclosure is in itself valuable. There are specific areas of complexity in the life sciences sector that make communication with the market potentially challenging, hence prompting AusBiotech and the ASX to produce the *Code* (first published in 2005 and updated in 2013), which is available from the websites of AusBiotech or the ASX.

9.7 Valuations

Valuing assets in the area of the life sciences, which are non-tangible, is an important and highly-specialised area, often requiring independent expert advice and beyond the scope of the Guide. A recommended resource is the book *Valuation in Life Sciences: A Practical Guide*²⁴ co-authored by valuation experts Boris Bogdan and Ralph Villiger. This book is the first complete guide to valuation in life sciences. It introduces the characteristics of life sciences development, and explains how to translate these into a valuation according to key models. Consultant groups are also available who specialise in valuation of biotech companies.

*products... the promotional side of business networking; persuading, or intending to persuade, prospects...; the process of promotion to build and sustain working relationships that relate to the business purpose.*²⁵

This description holds true in the life sciences, but the term often refers specifically to a specialist skill set and activities that prepare a company to, and attracts, investors, licensees and product partners, and in some cases, acquirers, joint venture or merge partners. It involves skills such as marketing, management, alliance management, commercialisation, licensing, valuation, investor relations, pitching, negotiating and crafting deals.

Companies that do not have this expertise on the board should seek professional advice from an experienced BD professional.

search for research expertise (that is, joining forces to confront challenges, manufacture and access marketing resources), commercialisation expertise (such as how to achieve regulatory approval with no experience) and/or financial support.

Each party to a partnership may be engaged in multiple partnerships and at times this may cause conflicts and/or tensions arising from differing priorities.

In most circumstances a university partner will bring more research and technical knowledge and less commercial experience and know-how than a commercial partner. A university partner will also have greater limitations on the scope of a partnership.

Traditional wisdom holds that biotechnology companies benefit from collaborations with their larger multinational peers, “which can help validate a company’s technology, provide capital to help fund clinical development, and enable access to experienced clinical, regulatory and commercial infrastructure.” However, the life sciences industry has matured in recent years and some companies have the capability and capital to develop and market their own products or to defer a partnership until the product is further along the development pathway in order to achieve a higher valuation.²⁶

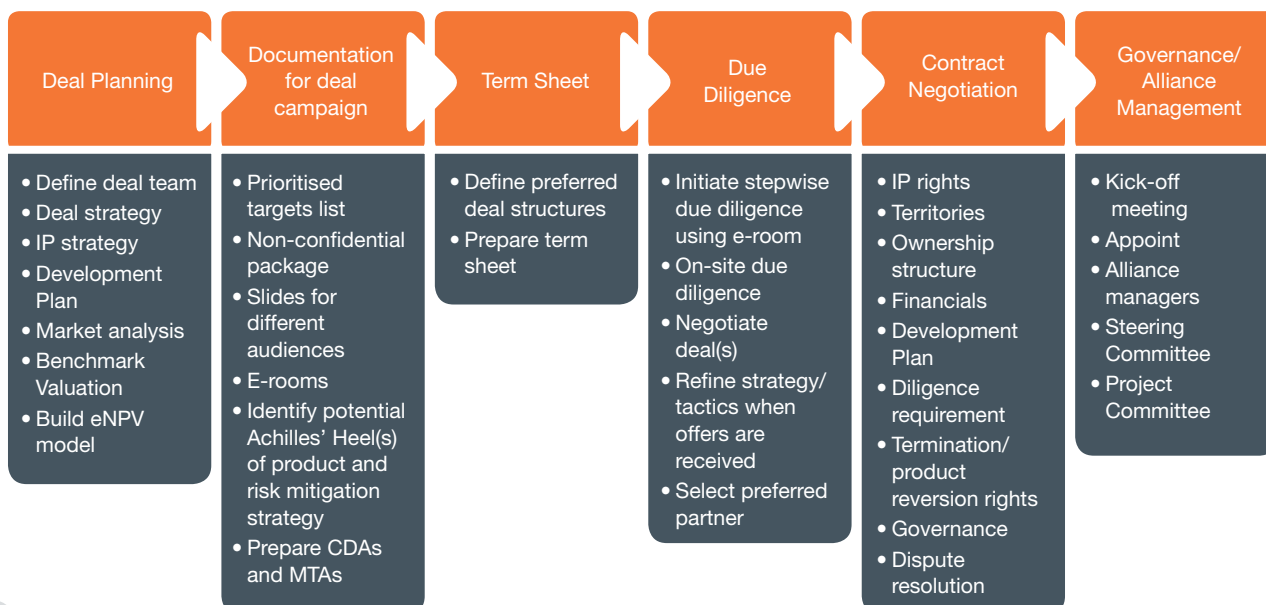
9.8 Business development

Business development (BD) can be described as: “*The activity that increases... the profit, production, or service potential of an enterprise; investment of capital and time that causes...the growth and expansion of an enterprise; the process of moving a business towards the point where it can provide its services and*

PARTNERING

Attracting partners and negotiating terms are key activities for a life science BD professional. Typically partnering occurs in relation to a product or platform technology, and ranges from partnering with universities and research institutes to partnering with multinational pharmaceutical companies. The motivations for such activities are to

Planning and executing a licensing campaign





TEN Intellectual property management

Most of the value of start-up life science companies will be attributable to their IP assets. For companies with a business model of licensing to third parties in return for royalties and other payments, a secure IP position will be a necessary condition for business success. It is therefore essential that IP assets are identified and managed in a way that maximises their value, and protects against risk. Potential investors and acquirers will review and validate a target company's IP portfolio and management systems, so it makes good sense to have these in order from the outset.

One of the key reasons for a focus on IP is the long lead time in life sciences from product conception to launch. IP assets that offer exclusivity or other competitive advantages assist in attracting investment and capital for technology development before revenue starts to be derived from sales or licensing.

While it can provide significant value, IP management is a specialist area requiring expert knowledge and substantial investment. For example, the management of one patent family (protecting a single invention in multiple countries) can cost at least \$25,000 per year during peak periods of expenditure, and the filing, worldwide prosecution

and worldwide maintenance of a patent family over its 20 year life could cost up to \$700,000, even if the patents are never enforced. The area is not intuitive and value can easily and unwittingly be destroyed by poor knowledge of the area. For a small company with concentrated IP assets, opposition to a patent application or litigation either enforcing a patent or defending its validity can be a make or break proposition.

Boards need to ensure that their company is using a reputable patent attorney to advise on patent strategy, and to prepare patent applications. This is not a substitute for the board itself taking a strategic approach to IP management, but recognises that effective use of patents is a highly-technical area. Typically, patent attorneys will have scientific or engineering qualifications, and will focus on patents for particular kinds of invention for example pharmaceuticals or medical devices.

Further information on IP in Australia is provided in the *Australian Government Intellectual Property Manual*: www.ag.gov.au/RightsAndProtections/IntellectualProperty/Documents/IntellectualPropertyManual.pdf.

10.1 What is intellectual property?

IP rights cover a range of exclusive rights that give a company the ability to maintain a competitive advantage, by protecting or establishing a monopoly over distinctive aspects of their knowledge and branding. These rights include:

- Patents for inventions such as drugs, devices and methods of treatment;
- Trade secrets and know-how, including proprietary processes, procedures, cell lines and information;
- Trademarks, brand names and logos; and
- Copyright materials (such as promotional materials and website content).

While not normally considered to be IP, other forms of protection may be obtained through regulatory exclusivity, or proprietary cell lines and other biological materials over which access can be restricted.

For most life science companies, patents, trade secrets and regulatory exclusivity will be of greatest importance. These are discussed further below.

10.2 Patents

Arguably the most important IP owned or licensed by a life science company is its patent portfolio.

Patents, the most common form of IP in life sciences, provide a registered monopoly on a defined invention for a period of time (generally 20 years). They provide the holder with the exclusive right to exploit the invention during the term of the patent, in exchange for fully disclosing the details of the process or product.²⁷

A patent may be granted where a device, substance, method or process which is new, inventive (that is, not obvious) and useful. In return for the grant of exclusivity, patent applicants must publicly disclose a full description of how their invention works, which can provide the basis for further research by others.

A patent provides the owner of an invention (the 'patentee') with exclusive rights for a limited time-frame. These exclusive rights allow the owner to exploit the invention claimed in the patent and to authorise a third party to exploit the invention.

Exclusivity is not automatic – a person must apply for and be granted a patent to obtain exclusive rights to exploit the invention. It is also possible for other parties to challenge the validity of the patent, resulting in a loss of exclusivity if the patent is revoked. The extent of the exclusive right (or monopoly) is defined in the detailed claims which form part of the patent specification.

There are two types of patents in Australia:

- A *standard* patent gives long-term protection and control over an invention for up to 20 years; and

- An *innovation* patent is a relatively fast, inexpensive protection option, lasting a maximum of eight years. Innovation patents are rarely used for life sciences inventions, given the short exclusivity period and the fact that they are granted (but not enforceable) without substantive examination.

It may also be possible in some countries to obtain additional protection for up to five years for pharmaceutical and biologics patents, in light of the time it takes to obtain regulatory approvals for such products.

In the US, a *design* patent is available to protect new and distinctive non-functional features of a three-dimensional product for a 14-year term. This kind of IP right is referred to as a registered design in most other countries.

Patent rights are specific to each country, although there is a streamlined process for making applications via the Patent Cooperation Treaty (PCT). The term 'patent family' is often used to describe patents obtained in various countries via a single PCT application. The ability to obtain patent rights, and the scope of the claims ultimately granted, may vary from country to country. For example, methods of medical treatment are not patentable in many countries, and recent court cases in the USA have denied patent protection to naturally occurring gene sequences and to diagnostic methods that amount to a monopoly over natural phenomena or 'laws of nature'. Life science companies need to understand what their key markets are, and any potential barriers to obtaining patent protection in those countries.

10.3 What can be patented?

A patent may be granted for a device, substance, method or process which is new, inventive and useful. It is not necessary that the advance be 'pioneering' a small improvement or variation over what is already known or used may be patentable.

Some subject matters that are *excluded* from patenting include:

- Human beings and the biological processes for their generation;
- Mere discoveries;
- Mixtures of known ingredients being used for their known properties in a medicine or food;
- Mathematical models, plans, schemes or other purely mental processes; and
- Inventions which are contrary to law.²⁷

It is not unusual for a technology to be protected by more than one patent family. For example, a technology may be protected by patents concerning composition of matter, method of manufacture, method of clinical use and/or synergistic pharmaceutical combinations.

In some jurisdictions, including Australia and the US, a *provisional* patent application can be filed up to 12 months prior to filing a patent application. The provisional application describes the invention without providing detailed claims or requiring inventor declarations and its content is not disclosed. The value of a provisional patent is that it can set a priority date 12 months earlier than the filing date. It will lapse however if a patent application is not filed within the 12-month period. A provisional patent application alone does not provide any enforceable rights.

10.4 Threats to patent protection

Applying for, and even being granted, a patent does not guarantee exclusivity. There are a number of grounds on which a pending patent application can be refused, or the validity of a granted patent can be challenged. As most action to enforce a patent results in a counterclaim of invalidity, life science companies need to take steps to address the likelihood of this occurring.

If an invention is demonstrated, (for example through a journal publication or conference presentation) sold or discussed in public before filing a patent application, the opportunity to patent it may be lost in many countries. Some countries, such as the US, allow a grace period (usually six to 12 months), however such a disclosure may invalidate the patent filings in other countries. Talking to potential contractors, business partners or advisers about the invention should only be done on a clearly 'in confidence' basis.

If the wrong inventors are named in a patent application, or the company is not legally entitled to own the invention made by the inventor(s), patent protection may well be lost.

10.5 Freedom to operate

Before commencing development of a product and before lodging a patent application, it is usually desirable to perform patent searches. Searches are required for:

- Seeking to ensure that a product will not infringe the rights of other patent holders; and
- Discovering existing information which relates to the invention, such as in earlier patent applications and journals, which may impact on the patentability of the company's invention.

Patent searches are not infallible, and are subject to time and resource constraints. Nevertheless, by adopting an appropriate search strategy, the chances of overlooking important documents can be minimised. Expert assistance should be obtained and searches should be ongoing. [Ref 27] Searching patent databases is also essential for understanding your competitors' patenting and product development strategies.

Regardless of whether or not patent protection is sought for your product or process, a third party may already have patent rights that restrict your

company's right to exploit its inventions. *Third party patent rights* also commonly affect life science companies' ability to use certain techniques in R&D activities. To avoid infringing such third party patent rights, your company may need to seek a licence. Alternatively, your company may be able to 'work around' a patent so as not to infringe patent rights. It is important to identify and address such 'freedom to operate' issues at the earliest opportunity.

The Australian Government in recent years legislated to enshrine in law an experimental use exemption on intellectual property. This reform was part of the 'Raising the Bar' Bill, passed into law in 2012. The exemption is designed to clarify that conducting research into the patented invention itself is not an infringement; but the exemption does not apply to conducting research using the patented invention to do research on something else. There is no general exemption from patent infringement for research organisations, in Australia or elsewhere.

The Intellectual Property Laws Amendment (Raising the Bar) Act 2012 clarifies the experimental use exemption. Under legislation, researchers are free to:

- Determine the properties of an invention;
- Improve or modify the invention;
- Investigate the validity of a patent or of a claim relating to the invention; and
- Examine whether a patent would be, or has been, infringed.

Researchers are free to do these things regardless of whether they are doing them under contract or with funding from a commercial entity or whether they are doing them with some commercial end point in mind.

They cannot market a patented invention or manufacture a patented invention for sale without the patent owner's permission. But all the research necessary to come up with a good idea, and confirm that it works, can be done without anybody's permission.²⁸

In Australia, the USA and certain other countries, there is also an exemption from patent infringement for activities directed to obtaining regulatory approval for the subject matter of a patent. This permits 'spring boarding', which is the practice of preparing to launch a competitor product (such as a generic drug) immediately after the patent protecting the originator version of the drug has lapsed.

10.6 Trade secrets

Trade secrets are useful for protecting information such as proprietary manufacturing or discovery processes, which can be difficult to protect by patent because they are constantly changing or evolving. However, any technology that has a good chance of being reverse engineered or found by others may be more appropriately protected by a patent.

No registration is involved, but the company safeguards the information by keeping it confidential and limiting the number of people who may access it, and by taking legal action in the event of any suspected or threatened breach of confidentiality. Keep in mind that in some countries it may not be possible to take such legal action, so taking practical steps to prevent unauthorised disclosure in the first place is always preferable.

Trade secrets and know-how may be protected by the courts where a duty of confidence is owed to the 'owner' of that information. A duty of confidence may arise because of a special relationship (like that between a company director and the company) or it may arise as a result of a contract that imposes specific obligations and restrictions. If there is any doubt as to the existence of such a duty, it is always better to clarify the situation by agreeing in writing as to how such information may be dealt with.

In order to protect trade secrets it is necessary for the information to be truly confidential. It is also important to ensure well-drafted confidentiality agreements are put in place with external parties such as collaborators and consultants.

10.7 Regulatory exclusivity

Regulatory exclusivity is tied to approval of a product (for example, a drug, medical device or veterinary product) and may come in a number of forms depending on the country in which regulatory approval of the product has been granted. Examples of these forms of exclusivity (defined in the Glossary of Terms section of this Guide) are:

- Data exclusivity;
- Marketing exclusivity; and
- Orphan drug status.

In a number of countries, including Australia, there is an interaction between patent and regulatory approval laws that provides for an extension of the term of a patent where a significant portion of the patent life has been used up in lengthy regulatory processes. The term of an Australian pharmaceutical patent may, if strict criteria are met and strict procedures are followed, be extended from the usual 20 year term to up to 25 years, provided that the extended term does not extend beyond 15 years from the date of regulatory approval.

10.8 Understanding the value of your company's intellectual property assets

It is important for directors to understand the potential and current value of a company's IP assets and to manage the asset to realise its value. This can involve adding value through further regulatory clinical trials, identifying alternative uses or indications, licencing, sale, valuation and understanding the product life cycle, market potential, competitors, legal protections and insurance. All of these aspects are discussed elsewhere in this Guide.

A typical IP strategy will include plans to build upon a core patent portfolio by submitting new patent applications and/or licensing or acquiring related IP that extend product protection beyond the term of current patents. As patent prosecution and renewal can become highly automated, from time-to-time it is wise to review a portfolio to decide whether it is necessary to continue to maintain all patents in a portfolio.

The company should have a clear understanding of how its patents and other IP rights fit into and are relevant to its product portfolio, and the scope of its monopoly rights. A patent portfolio that looks impressive on paper may not in fact protect a particular product of the company, either because the patents do not cover the product, or do not cover an easily available workaround. Understanding a company's key markets is crucial to registering the appropriate patents.

10.9 Managing intellectual property assets

IP management involves implementing systems to identify, record, use, value, protect and exploit IP in an efficient and effective manner. An example of a common tool for a company's IP management is a register of pending and granted patents and an IP management policy, both of which are periodically reviewed by the board.

In contrast to most other forms of property, IP is intangible and may be more difficult to identify and manage than tangible forms of property. Without proper management, companies may be unaware of the existence of IP, may not recognise its value or benefits, or may unintentionally expose themselves to risk. By managing IP systematically, companies are able to maximise the IP's operational and strategic utility, and minimise the risks of third party abuse or accidental loss or infringement.

One key element of IP management is ensuring that the company can demonstrate good title to its IP rights.

This involves appropriate treatment of employment and consultancy contracts, sound record keeping, and ensuring that any collaborative research projects are the subject of clear and comprehensive contracts. Potential investors, licensees and acquirers will need to be able to verify that the company owns or controls assets that are key to the company's valuation and future prospects.

IP management is most effective when incorporated into a company's existing asset management systems and processes. It does not require the creation of a whole new framework or infrastructure, and will generally not result in a substantial ongoing drain on current resources.

As discussed in other parts of this Guide, life science companies will typically need to partner with larger organisations in order to bring a product to market. Therefore life science company boards need to understand the essentials of IP licensing, and ensure that the management team includes business development expertise for structuring and negotiating licences. In particular, boards need to consider what rights they should reserve to the company, and what rights they should allow to the other party, to deal with new intellectual property, or improvements to existing intellectual property, that is developed in the course of a licensing or partnering arrangement.

While it may seem 'balanced' to provide that IP developed in collaboration with others is 'jointly owned', such a structure can lead to difficulties if in future the parties have differing views about how and where to exploit that intellectual property. Intellectual property is a very flexible asset – it is possible to grant a variety of rights, without giving up ownership or control by, for example, granting licenses to use intellectual property for particular applications or in particular countries or regions. Boards need to access expertise, internally or from outside, in order to take a strategic approach to IP licensing.



ELEVEN Managing risk for a life science company

11.1 Risk management

Understanding a company's risk and actively monitoring, managing and mitigating such risk is an essential activity for any board. However, a number of risks are typically amplified, some by an order of magnitude, in the life science arena. Because the risks can be greater, the importance of identifying and actively developing and delivering contingency and mitigation strategies is greater as well. Commensurate with the heightened risk profile of a life science company, its board members are therefore required to have a matched and appropriate, often greater, acceptance and tolerance of and appetite for risk.

The following risks are considered the key risks that a life science company may encounter:

SIZE-RELATED RISK

The types of risk and the mix of risks a company is exposed to as well as the level of such risks will change over the life cycle of a company. For example, the risk profile of a start-up company with only one technology and no revenues will be vastly different from that of a mature company with a broad portfolio and product/s on the market and cash reserves. In the former case,

the failure of clinical trial to meet its endpoint could cause the demise of the company, whereas in the later case it may instead be an unwelcome, but only partial, setback.

FINANCIAL RISK

Availability of capital and sufficiency of funding to develop the technology of the company poses a significant risk for a life science company, especially if the company is in the pre-revenue phase. The cost of development of biotechnologies often runs into the tens of millions of dollars, sometimes hundreds-of-millions or even billions, before the company will have the opportunity to earn revenue from its technology.

The company may need to raise funds from time-to-time to meet its next milestone, such as the next phase in a trial, and its ability to operate in certain circumstances will be subject to its ability to raise capital. The ability to raise capital will be subject to a range of factors, some internal and some external. Internal factors might be the progress of a technology toward regulatory approval, or the calibre of the board. External factors that should be monitored might include changes in regulatory requirements or competitor products in development. Some external factors will be beyond the control of the company and its directors, such as the health

of economies globally or the international currency exchange rate.

INTELLECTUAL PROPERTY AND MARKET EXCLUSIVITY

As noted in the IP Section of this Guide, the value of a life science company will typically be attributable to its IP assets. It is therefore essential that IP assets are identified and managed in a way that maximises their value, and protects against risks. The commercial value of technology is dependent on legal protections, most often patents, provided by IP rights, or market exclusivity rights, or a combination of both.

For companies with a business model of licensing to third party manufacturers in return for royalties and other payments, a secure IP position will be a necessary condition for business success.

The establishment and management of IP protections in the life sciences is a highly-specialised area, and an expensive exercise. These legal mechanisms, however, do not guarantee that the technology will be protected or a company's competitive position maintained. There are risks that IP rights will be breached or challenged. These risks are heightened by the various differing provisions and enforcements in other countries. For example, patent protection may not be sought

in all countries either because such protection might not be commercially practical or because patent protection may be unavailable or limited in certain countries.

HUMAN RESOURCES AND KEY PERSONNEL

From a founder-run company to a large multinational company, the attraction and retention of effective management is critical. In the life sciences, the scientific personnel are also critical and this role is sometimes filled by specialist expert advisor/s. More often though, it is important for key personnel to be proficient in both commerce and science. For a start-up company, in particular, the key personnel often have highly-specialised knowledge of the technology in development, but may lack other skills.

A founder who is heading a company poses two types of risk: the risk of leaving the company, without sufficiently imparting of their specialised knowledge, and the risk that a founder's personal investment and limitations may hold back the company's development or growth.

TECHNOLOGY DEVELOPMENT

There are many risks inherent in the development of life science products including that they may fail during clinical trials or may fail to gain a regulatory authority's approval. There are large risks associated with development work being undertaken, and it is unknown if the development of any product will ultimately be approved for marketing or be commercially successful. In the biotechnology field, the time taken to develop and obtain regulatory approval for marketable products is long, potentially as long as ten years or more, and consequently subject to inherent risk.

Research is often outsourced to a contract research organisation, and the quality of the research and clinical results will therefore depend on the technical competencies of the staff at such an organisation. This is equally

important for contract manufacturing, which is a common activity in the life science sector.

Another issue in the development of a technology is the ability to value it in a commercial sense, either for the attraction of capital investment or for potential licensing to third parties. Valuation of intangible assets is a specialist area and discussed in section 9.7.

CONTRACTS

Many life science companies operate a virtual organisation business model, with outside companies being brought in to provide specialised services to the firm. Additionally there is a high degree of collaboration and in-licensing of technologies from other firms and research institutions to assist with moving a project through the development phase to commercialisation.

Such activities are typically transacted through contractual arrangements which, if not correctly prepared or managed, can adversely impact the life science company. For example, delaying a project due to inadequate dispute resolution processes, weakening IP positions through inadequate provisions around ownership of new discoveries, or inadvertently assuming the liabilities of the outsourced organisation or collaborator.

To manage such risk, processes need to be in place to ensure all contracts are appropriately vetted to best protect the life science company's interests in the event of a dispute or performance failure. For contracts that are critical to the commercialisation project, and arguably all contract, professional legal opinion should be obtained.

REGULATORY

The development of a life science-based product is usually a highly-regulated process and a critical barrier to market is the regulatory approval required for marketing the product. There are likely to be a

number of events and issues arising during a company's progression down the development path that will pose risk to the company. Country-specific regulatory processes are present in most countries; however some countries will rely on approval from another jurisdiction. Failure to achieve regulatory approval effectively blocks a product from entering a market.

Even after regulatory approval, unforeseen adverse events or manufacturing defects may arise in biologically-based products, which could expose a company to issues such as product liability claims or litigation, recall, harm to users, environmental impacts or public controversies.

Many of these occurrences can result in the suspension or removal of the regulatory approval for the relevant products and/or monetary damages being awarded against the company. Life science companies should ensure they are compliant with the appropriate prevailing quality assurance and quality control guidelines and active on pharmacovigilance.

COMPETITION

A company's future success will depend on its ability to develop technologies that are competitive and sought-after in the market place. While IP protections and complexity of biotechnologies act as barriers to competitors, competition can diminish or void the value of an asset. For example, a follow-on treatment for cancer may find itself with a number of alternative therapies in development at the same time. Being the first to regulatory approval or the preferred option, due to the mode of action or a better side effect profile, may block the market for others.

Also, a product needs to have a defined group of customers that will see the product as valuable. Developing a product for which there is already a better alternative will end in commercial failure.

GxP COMPLIANCE

A life science company is required to adhere to a range of operating standards from research through manufacturing and supply. These include GLP, GMP and CMC (as discussed in section 6) as well as Good Clinical Practice (GCP), and Good Distribution Practice (GDP), collectively known as GxP. Many of these standards are derived from the ICH Guidelines (see section 7.5) and are designed to assure the quality, safety and efficacy of products, and form the basis for regulatory assessment of product approvals and facility operating licenses. Life science company directors should understand how GxP compliance is maintained throughout a product's lifecycle and across its supply chain. GxP failure can materially impact the company. For example, failure of a clinical trial site to maintain GCP compliance can invalidate the results of a trial, preventing them being used to secure regulatory approval; and failure of a contract manufacturing site to maintain general site GMP, or GMP in relation to other products made there, can result in supply interruptions and/or a refusal of regulators to grant new approvals of any product made in that facility.

11.2 Mitigating risk

It is common and desirable for boards to monitor risk on an ongoing basis; seeking to understand and evaluate risk and the changes in risks and risk profile for the company over time. Due to the heightened risk profile of a life science company, it is recommended that directors pay particular attention to risk management, and include it as a standing item at every board meeting.

A director who is new to a life science board is advised to enquire about the:

- Board's charter, terms of reference and governance framework;
- Working relationship amongst the board members;

- Experience of others working with individual board members;
- Standard operating procedures, such as the financial management plan, the disaster recovery plan, and the project management plan/s (each project should ideally have a unique charter and contingency plan); and
- Risk mitigation framework, including its risk register. A typical risk register might identify risks such as finance, governance, management, communications/media, project, culture, community, and competitor activity; a risk ranking matrix (likelihood versus consequence); and the associated mitigation strategy.

It is also usual for a board to have a risk and audit sub-committee with terms of reference, including responsibility for monitoring financial risks, which would involve a 'going concern' test to mitigate insolvency and determine the levers available to adjust the company's cost base. To manage risk, some companies will run two budgets: a 'winding down' budget and a 'going concern' budget, which the risk and audit sub-committee would monitor and review and report back to the board regularly.

11.3 Life science related insurances

One of the strategies companies use to manage risk is to transfer it by taking out insurance policies. Many of the relevant insurance products are common to most businesses, such as workers' compensation insurance or corporate travel insurance – or in large companies 'key man' insurance against loss or kidnap of key executives. However, in the life science sector, some risks are unique to life science companies, such as those presented by clinical trials.

It is vital that a company provide adequate disclosure to their insurer to ensure that they have adequate

risk coverage, and choosing an insurer with life science experience is recommended. To ensure risk coverage remains relevant to each phase of a company's development, a regular review of the assumptions underlying the insurances should be conducted.

There are at least four insurance products to be considered by a life science company. These are: directors and officers liability insurance, clinical trials liability insurance; IP insurance; and product liability insurance. The company will need to determine who needs to be covered and who can be covered by the policy, for example, subsidiaries, controlling interests, lessors of premises or equipment, contracted individuals or companies performing work for the firm.

Additionally, life science companies need to be aware that the coverage provided by these products can vary considerably from insurance company to insurance company, and that not all companies will have experience in handling the more challenging claims, which life science firms can make or have made against them. Boards should take the time to ensure their insurance portfolio effectively transfers the desired exposures off the firm's balance sheet and onto their insurers, and that such insurers have the appropriate expertise to effectively manage a claim, should the unforeseen arise.

DIRECTORS AND OFFICERS LIABILITY

Given the high risk of a technology not being commercialised and the prevalence of Australian life science firms listing on the stock exchange to raise capital in the R&D phase, it is paramount that boards consider insurance to protect the company in the event of shareholder or investor litigation. Director's and officer's liability insurance is designed to cover such circumstances.

Critical areas of coverage which should be considered include:

coverage of the life science firm as a legal entity (often called 'Side C' cover); a 'hammer clause', where an insurer will cap their payout to an amount for which they can settle the action when the directors and officers wish to continue defending themselves and the business; and the ability of the insured to select their own defence counsel and extensions to cover employment practices liability.

For companies with no revenue stream from commercialised technologies, exclusions around insolvency will be applied. Depending on the strength of the firm's balance sheet, the rate of cash burn in the firm and the composition of the firm's shareholders or investors, such exclusions can be removed on a case-by-case basis.

CLINICAL TRIALS INSURANCE

Many countries including Australia have compulsory insurance requirements for commercial sponsors of human clinical trials, which can vary considerably from jurisdiction to jurisdiction. For example, most states and territories in Australia require \$10 million worth of coverage, and most EU countries will require some form of policy issued by an insurer located in the country where the trial is taking place. This type of insurance is typically used to compensate participants in a clinical trial, who experience harm from the trial. Trials are often multi-national making the insurance requirements complex.

Early engagement with insurers is desirable in the clinical trial planning phase, to minimise or avoid additional expense or delays to ethics committee submissions. The level of cover should be consistent with partners' and licensees' obligations.

IP INSURANCE

It has been highlighted in the 'Intellectual Property and Market Exclusivity' section of this Guide that it is essential that IP assets are identified and managed in a

way that maximises their value and protects against risks, however legal mechanisms for protection of IP do not guarantee that the technology will be protected or a company's position is maintained as there are risks that the IP rights could be breached or challenged.

Invariably for a life science company, its IP rights and technology form the core of its assets within the business. Insurance, while not commonly used in Australia is available to protect such assets and cover can be structured to manage and mitigate potential risks such as:

- Ownership risk to pursue infringers of owned/licensed IP rights;
- Trading risk to protect against the potentially ruinous damages and substantial legal costs involved in an action brought against the company for infringing third party IP rights;
- Contractual risk to fund legal costs involved in an action either pursuing or defending a contracting party; and
- IP value risk to protect the income of an enterprise against the risk of a legal challenge preventing the sale of a company's goods or services or the exploitation of the IP rights.

PRODUCT LIABILITY INSURANCE

For life science firms with commercialised products or licensed technologies being used in other firms, commercialised product protection needs to be considered for liabilities arising from bodily injury or property damage to third parties caused by their product.

Product liability insurance is designed to cover this exposure. Elements of coverage that should be considered include cover for expenses associated with product recall, liabilities of third parties assumed in a contract or agreement, and cover for pure economic loss due to a defect or deficiency in the product.

If the product is being exported or sold overseas life science firms also need to consider global liability extensions to integrate their insurance with any local admitted insurance purchased in countries where the product is being sold.

Most specialist insurers also provide cover on a claims-made basis (meaning the policy is triggered when the claim is made against the firm, not when the injury or damage happened, which gave rise to such a claim). Consideration therefore needs to be given to the availability of extended reporting periods and how the policy treats adverse event notification when testing for knowledge of circumstances that could give rise to a future claim.

PROPERTY INSURANCE

While property insurance is common in many businesses, life science companies are exposed to specialised risks which may not be adequately addressed by a standard property insurance policy.

Areas of coverage which need to be considered include cover for the value of scientific animals used in research, production or breeding programs, spoilage of temperature-sensitive materials, damage caused by contamination or special pollutants (for example, radioactive materials) and business interruption cover for funding that may not become available due to missed milestones following a fire or other incident which damages the life science firm's property or premises.

More common, but equally important, is protection for company stock or materials stored at third party locations, and cover for stock or materials in transit (for example, marine transit insurance).

TWELVE Glossary of terms

Abbreviated New Drug Application (ANDA)

An ANDA contains data that provides for the review and ultimate approval of a generic drug product by FDA. Generic drug applications are abbreviated because they are not required to include preclinical and clinical data to establish safety and effectiveness. Instead ANDA applicants must be able to prove clinically that the generic product is bioequivalent; that is, it is likely to perform in the same manner as the original drug based on measures of safety and efficacy.

Bioavailability

The degree to which a drug becomes available to the target tissue after administration

Bioequivalence

Two drugs that have the same potency and bioavailability, assuming equal doses, are said to be bioequivalent.

Clinical trial

Trials performed in human subjects to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are typically in four phases: Phase 1 tests a new drug or treatment in a small group; Phase 2 expands the study to a larger group of people; Phase 3 expands the study to an even larger group of people; and Phase 4 takes place after the drug or treatment has been licensed and marketed. A more recently-introduced Phase 0 is used by the FDA and refers to exploratory, micro-dosing studies.

The Code

The Code of Best Practice for Reporting by Australian Life Science companies, Ed 2, 2013, was developed jointly by ASX and AusBiotech.

Conflict of Interest

A conflict of interest is any situation that puts a director in a position to abuse their role for personal or business gain. If a particular decision is likely to benefit a director in any way, or benefit someone close to a director, that director is no longer in a position to make an impartial decision and he or she has a conflict of interest.³⁰

Control group

The standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

Data exclusivity

A period of exclusivity granted to an innovator by a regulatory body (such as the FDA) at the time of approval of a new product. During the period of data exclusivity, generic competitors are prevented from relying on data generated by the innovator to secure regulatory approval for a generic or biosimilar version of the innovator drug.

Double blind study

A clinical trial design in which neither the study subject nor the study staff know which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce more objective results, since expectations do not affect the outcome.

Drug candidate

A compound selected from the lead optimisation process and identified for formal development.

Efficacy

The ability of a drug or treatment to produce a desirable treatment result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and in treating the illness for which it is to be prescribed. In the procedure mandated by FDA, Phase 2 clinical trials gauge initial efficacy

and safety (typically through testing a range of doses), and Phase 3 clinical trials confirm the efficacy and safety of the dose and frequency of dosing to be approved.

Food and Drug Administration (FDA)

A US government agency responsible for the evaluation and approval of all new drugs and generic drugs. More generally, FDA is responsible for protecting public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food, cosmetics and products that emit radiation.

Formulation

The active pharmaceutical ingredient and its various non-active carriers, binders, stabilisers etcetera.

Freedom to Operate (FTO)

A status which indicates that the commercial production, marketing and use of a new product, process or service does not infringe the IP rights of others.

Generic

A generic drug is one that is bioequivalent to an original drug.

Good clinical practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Good laboratory practice (GLP)

Quality systems that apply to the conduct of preclinical studies, typically safety and efficacy studies in animals.

Good manufacturing practice (GMP)

A standard governing the manufacture of human and animal drugs and biologics.

Human Research Ethics Committee (HREC)

A committee that provides guidance in meeting obligations for the effective governance of research involving humans. The role of an HREC is to provide an ethical review of the proposed research including consideration of the scientific design of a study, how participants will be recruited, the care and protection from harm of research participants and protection of research participants' confidentiality. All human research conducted in Australia must undergo ethical and scientific review, approval and monitoring by a HREC registered with the Australian Health Ethics Committee (AHEC) and operating in accordance with the National Health and Medical Research Council.

Inclusion/exclusion criteria

The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria define the patient population to be studied and are based on such factors as age, gender,

the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.

Indication

The approved use for a specific drug.

Institutional Review Board (IRB)

A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the US must be approved by an IRB before they begin. Every institution that conducts or supports biomedical or behavioural research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

Intent to treat

Analysis of clinical trial results that includes all data from participants in the groups to which they were randomised even if they never received the treatment.

Investigational Device Exemption (IDE)

FDA regulations under 21 CFR 812 for which an approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21CFR 812 are met.

Investigational New Drug Application (IND)

An application to the US FDA to begin studies of a new drug or biologic on humans. The IND gives the plan for the study and contains formulation, manufacturing and animal test result information.

In Vitro

Outside a living organism.

In Vivo

Within a living organism

Lead (compound, product or molecule)

A compound, product or molecule that is suitable for further optimisation.

Lead optimisation

The process of chemically modifying and subsequently testing lead compounds so that desirable characteristics can be introduced into the molecules.

Marketing exclusivity

A period of exclusivity granted to an innovator by a regulatory body (such as the FDA) at the time of approval of a new product. During the period of marketing exclusivity, the regulatory body cannot allow a competing generic product to enter the market. The key difference

between data exclusivity and marketing exclusivity is that a competitor cannot circumvent marketing exclusivity by generating its own data and submitting a new application for regulatory approval.

Medical device

Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease;
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- Investigation, replacement, modification, or support of the anatomy or of a physiological process;
- Supporting or sustaining life;
- Control of conception;
- Disinfection of medical devices; and
- Providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

New Drug Application (NDA)

An application submitted by the manufacturer of a drug to the FDA after clinical trials have been completed for a licence to market the drug for a specified indication.

Non-clinical studies

Drug development studies including formulation, optimisation and investigations in vitro and in animals to assess dose, efficacy, pharmacokinetics and safety before human clinical trials. Includes preclinical studies. The term non-clinical studies also includes toxicology. Note that non-clinical studies generally infers formal GLP studies undertaken in support of an IND (or equivalent) filing. Preclinical studies may or may not be non-clinical studies, depending on whether they are conducted in support of a regulatory filing.

Non-clinical toxicology

The testing of new drug candidates for toxic effects in animals, prior to testing in human clinical trials.

Open label study

A clinical trial in which doctors and participants know which drug or vaccine is being administered.

Orphan drug status

An FDA category that refers to medications used to treat diseases and conditions that occur rarely. Orphan drug status gives a manufacturer specific financial incentives

and market exclusivity to develop and provide such medications.

P-Value

The probability value (p-value) of a statistical hypothesis test used to determine the meaningfulness of results in clinical trials versus a control group. The smaller the p-value, the more statistically significant the result. Generally a p-value of ≤ 0.05 in a clinical trial result is considered to show statistical significance. This means that there is less than a 5% probability of the result occurring by chance, and therefore a 95% probability that there was a real effect of treatment. In general, results with p-values above 0.05 are not considered statistically significant.

The p-value should be put in the context of the test type used and how the p-value is derived.

Patent

A property right granted by the Government of the country or territory where the patent is held, to an inventor “to exclude others from making, using, offering for sale, or selling the subject invention throughout the country or territory where the patent is held or importing the invention into the country or territory where the patent is held” for a limited time in exchange for public disclosure of the invention when the patent is granted.

Patent application

There are two types of patent applications: provisional and non-provisional. A non-provisional application establishes the filing date and initiates the examination process. A non-provisional utility patent application must include a specification, including a claim or claims; drawings, when necessary; an oath or declaration; and the prescribed filing fee. A provisional patent application allows filing without a formal patent claim, oath or declaration, or any information disclosure (prior art) statement. It provides the means to establish an early effective filing date and automatically becomes abandoned after one year. It also allows the term ‘patent pending’ to be applied.

Patent family

The same invention disclosed by a common inventor(s) and patented in more than one country.

Patent filing date

The date of receipt in the patent office of a patent application.

Patent granting date

The date on which the patent is granted by a particular patent office. Note that the same patent will have different grant dates in different countries.

Patent infringement

The unauthorised making, using, offering to sell, selling or importing into the country or territory where the patent is held of any patented invention.

Patent pending

A phrase that often appears on manufactured items. It means that someone has applied for a patent on an invention that is contained in the manufactured item. It serves as a warning that a patent may be issued that would cover the item, and that copiers should be careful because they might infringe if the patent is issued. Once the patent is issued, the patent owner will stop using the phrase 'patent pending' and start using a phrase such as 'covered by US Patent Number XXXXXX.' Applying the patent pending phrase to an item when no patent application has been made can result in a fine.

Peer review

Review of a clinical trial by experts. These experts review the clinical trials for scientific merit, participant safety, and ethical considerations.

Pharmacokinetics

The concentration profile of a drug and its metabolites in different parts of the body over a period of time. The concentrations typically depend on the dose and the rate of absorption, distribution, metabolism and excretion.

Pharmacovigilance

Pharmacovigilance refers to the practice of collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.

Phase 1 clinical trial

A clinical trial, usually in normal healthy volunteers, to assess drug safety, tolerability and pharmacokinetics.

Phase 2 clinical trial

A clinical trial in the patient population, typically to assess initial safety, tolerability, pharmacokinetics and preliminary efficacy data.

Phase 3 clinical trial

Large clinical trial across multiple centres to assess conclusively the efficacy and safety of a drug in treating a specific disease.

Phase 4 clinical trial

Post marketing evaluation of a drug to ensure adverse events are reported and to build up a complete safety and efficacy profile for the drug.

Placebo or vehicle controlled study

A method of investigation of drugs in which an inactive substance or drug vehicle (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is safe and/or effective in treating the condition.

Placebo

A substance that has no known therapeutic effect, used as a control in testing new drugs.

Pre-market approval (PMA)

An approval from the FDA for a medical device.

Preclinical studies

Drug development studies including formulation, optimisation and investigations in vitro and in animals to assess dose, efficacy, pharmacokinetics and safety before human clinical trials.

Preclinical toxicology

The testing of new drug candidates for toxic effects in animals, prior to testing in human clinical trials.

Randomised study

A study in which participants are randomly (that is, by chance) assigned to one of two or more treatment or placebo arms of a clinical trial.

Scientific Advisory Board (SAB)

A board that advises on clinical and/or scientific matters.

Side effects

Any action or activity outside the intended therapeutic effect of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects. It is important to note that in patients, it is frequently difficult to distinguish between adverse effects caused by the drug and those inherent in the disease. The use of blinded clinical trials comparing the active ingredient versus placebo attempts to overcome this problem.

Single blind study

A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking; also called single-masked study.

Sponsor

The company, research institution, or healthcare organisation that funds a clinical trial and designs the protocol. The sponsor must be incorporated in the territory where the clinical trial is being undertaken (e.g. sponsors for Australian clinical trials must be companies or institutions that are registered in Australia).

Statistical significance

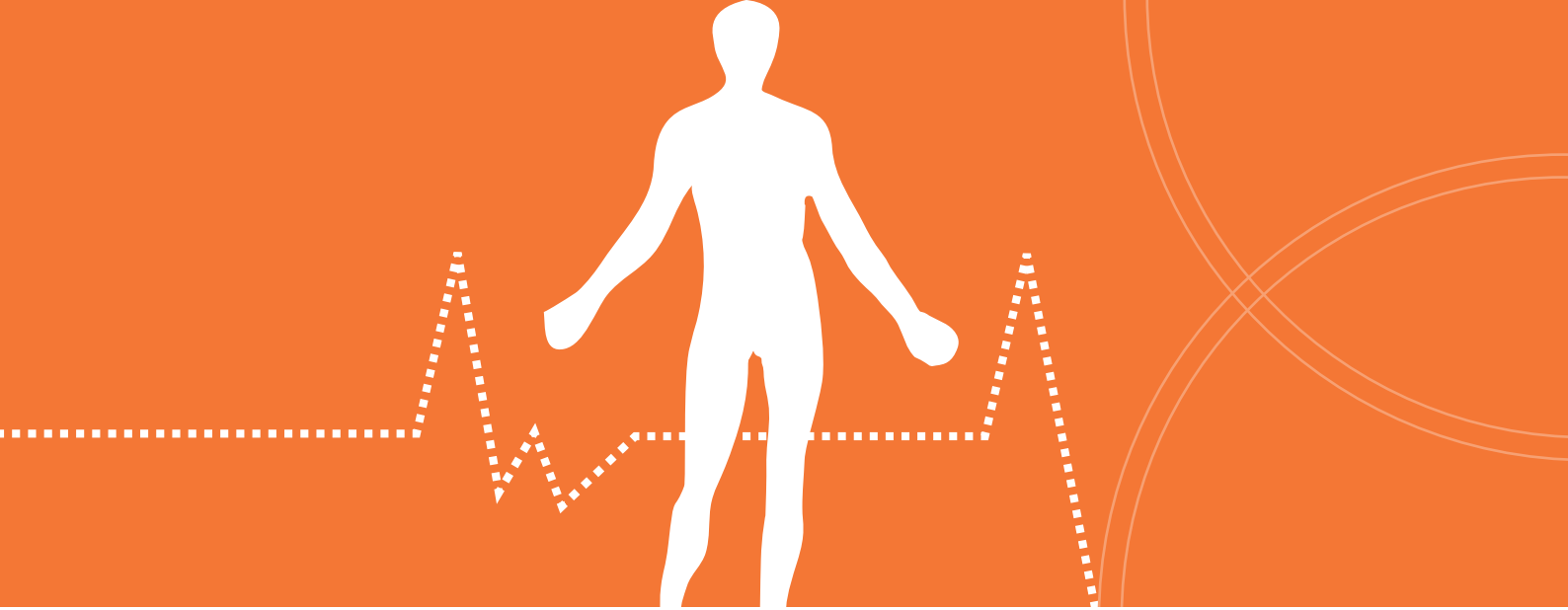
The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends among other things on the number of participants studied and the observations made, as well as the magnitude of differences observed and the variation between subjects.

Study endpoint

A primary or secondary outcome used to judge the effectiveness of a treatment

Toxicity

The degree to which a drug is poisonous or has an adverse effect on an organism.



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As a commercial lawyer, she engages early with her clients on their structure, governance, operations and strategy. Building long-term relationships, she invests in understanding her clients' culture

and priorities so that her advice is timely and practical. Lis is a member of AICD and regularly presents on governance topics including board evaluations, continuous disclosure and directors' roles and responsibilities. Her skills include advising on board dynamics and planning for complex AGMs.

Lis is also Chair of the NSW Committee of AusMedtech, an advisory group to AusBiotech, dedicated to the advancement of the Australian medical technology industry.

Dr Andrew Bray, Chief Executive Officer, Elk OrthoBiologics

With a background in science innovation, business development and management, Andrew has been actively involved in the biotechnology industry in Australia, USA and Europe since 1988.

Following a period at CSL Limited, a large part of his career was spent at Chiron Corporation, one of the first successful US biotech companies, and Chiron Mimotopes, where as Chief Chemist he played a key role in establishing and leading a profitable Australian peptide and chemistry discovery business with an international reputation. Andrew's work in drug discovery, peptide

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More recently Andrew has been involved in building Australian-based biotechnology companies Broadvector Limited and subsequently Elk OrthoBiologics Limited, currently focusing on the clinical application of a novel gene therapy to orthopaedic conditions where there are few treatment options.

Andrew received a PhD in organic chemistry from the University of Melbourne and undertook executive education at Monash Mt Eliza Business School.

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Lorraine has worked as a dedicated advocate for the biotechnology sector since joining AusBiotech almost five years ago as the Manager of Communications. In this role she works closely with public policy impacting the sector and provides

communication via various mediums to inform AusBiotech members and key stakeholders about industry news. She is Editor of *Australasian Biotechnology*, AusBiotech's quarterly journal, and writes regularly for a range of industry publications.

Lorraine has previously worked in corporate affairs for a multinational biopharmaceutical company as well as in communications roles for The Pharmacy Guild of Australia and the University of Melbourne. She has also worked for a health consumer organisation as an advocate.

Lorraine has an undergraduate degree in public relations, majoring in journalism, a postgraduate diploma in marketing, and an MBA from the University of Melbourne's Melbourne Business School.

Dr Leigh B Farrell, Vice President Business Development, Biota

Leigh was appointed Vice President, Business Development in 2006. Prior to joining Biota, Dr Farrell spent approximately four years as an Associate Director at GBS Ventures Partners Limited, a specialist Life Sciences Venture Capital Fund.

Leigh previously held the positions of Research Manager at Johnson & Johnson Research Pty Ltd and Chief Executive Officer of Gene Shears Pty Limited. He has extensive international experience in corporate finance, business development, licensing, relationship management and intellectual property portfolio management in the biotechnology and pharmaceutical industries. He is currently the Chairman of the Competitive Business Environment Working Group established under the 2007 Biotechnology Strategic Development Plan for Victoria.

Ms Dominique Fisher, Managing Director, Helix Digital
Dominique was appointed a non-executive director of Circadian

in September 2005. She became Chairman of the Board in the subsequent month and is a member of the Company's Audit and Risk Committee. She has extensive business experience in the corporate area, including the commercialisation of new technologies.

Dominique is Principal and Executive Director of EC Strategies Pty Ltd, which advises local and offshore companies on technology strategies and major commercial transactions. She is Managing Director of Helix Digital Pty Ltd and is the Executive Chairman of CareerLounge Pty Ltd. Her past appointments have included a non-executive director of Pacific Brands Limited and membership of its Audit and Risk Committee, Chairman of Sky Technologies Pty Ltd, Councillor of the Australia Council of the Arts, and Chairman of its Dance Board, Insurance Australia Group Limited (IAG), member of the Prostate Cancer Foundation Victoria, NRMA, the Malthouse Theatre, Sydney Opera House and member of the ICT Advisory Board, advising the Federal Government on key issues affecting the development of the information technology and communications sector.

Mr Lawrence Gozlan, Chief Investment Officer, Scientia Capital

Lawrence was the founder of Scientia Capital, a specialised global investment fund focused exclusively in life sciences which manages investments for institutional investors, family offices and high net worth individuals.

Prior to this, Mr Gozlan was responsible for the largest biotechnology investment portfolio in Australia as the institutional biotechnology analyst at QIC (Queensland Investment Corporation), an investment fund with over AU\$60 billion under management. He previously was the senior

biotechnology analyst at Foster Stockbroking, and advised numerous life science companies in corporate finance at Deloitte. Mr Gozlan is a board member of several public and private healthcare companies, and has presented at numerous international life science conferences. He holds a Bachelor of Science with Honours in microbiology and immunology from the University of Melbourne specialising in neurodegenerative diseases.

Dr Anna Lavelle, Chief Executive Officer, AusBiotech Ltd

Anna was appointed inaugural Chief Executive Officer of AusBiotech Ltd in June 2005. Previously Dr Lavelle was an Executive with the Australian Red Cross Blood Service (ARCBS) commencing in 1998 as Director responsible for Strategic Planning and Business Development. In 2002, Dr Lavelle was appointed Director of Intellectual Capital and was responsible for management of the national R&D program, evaluation of emerging technologies and international and national business development activities including technology transfer and IP management.

Prior to joining ARCBS, Dr Lavelle held positions of Chief Executive Officer of a public health organisation, Industry lobbyist for a member organisation and was an academic at Monash University, Melbourne. Dr Lavelle holds a Doctor of Philosophy in Genetics from the University of Melbourne.

Ms Julie Phillips, Chief Executive Officer, BioDiem

Julie has a strong background in the biotech and pharmaceutical industry, having worked as the CEO and director of start-up Australian biotechnology companies operating in the life science sector. Her technical background in clinical trials, regulatory affairs and

pharmacoeconomic assessment/ pricing of therapeutics was gained in multinational pharmaceutical companies with responsibility for market entry of new products in Australia and New Zealand.

Ms Kate Spargo, LL.B. (Hons), B.A., FAICD

Kate has over 15 years of experience in non-executive directorship roles, mainly in the finance, infrastructure, and professional services sectors and currently holds or has held non-executive directorships with listed companies UGL Ltd; Sonic Healthcare Ltd; Investec Bank (Australia) Ltd; ColInvest Ltd; Fletcher Building Ltd; SMEC, an international engineering consulting firm; and Griffith Hack, a patent attorney firm, among others. A particular focus for her in these roles is related to business ethics and governance, and in developing and sustaining business operating standards. She also chairs or is a member of the Audit, Risk, and/or Remunerations Committees for many of these companies.

Kate is a Fellow of the Australian Institute of Company Directors. She has qualifications in law and arts from Adelaide University. Kate has been a public member of the International Ethics Standards Board of Accountants since 2010 and was nominated by the Accounting Professional and Ethical Standards Board (APESB) in Australia.

Associate Professor Jan Tennent, CEO, Bio21 Cluster

Appointed in January 2012, Jan is the Chief Executive Officer of the Bio 21 Cluster, Victoria's leading biomedical and health sciences research cluster of organisations with international strengths in biomedical research, healthcare and education. With extensive experience in research and commercialisation, Jan previously held leadership roles with CSIRO, the CRC for Vaccine Technology, CSL and Pfizer where she was the Director of Business Development & Global Alliances for the animal health business in Asia Pacific.

Jan is a Trustee of the Licensing Executives Society of Australia and New Zealand and Director of two family-owned companies. Previously she was a Board member of Tweddle Child and Family Health Service (2011-2013) and on the Council of Melbourne High School (2011-2013).

Jan is a Principal Fellow in the Department of Microbiology & Immunology at the University of Melbourne and a Fellow of the Australian Society for Microbiology. Jan holds a Doctor of Philosophy in Microbiology from Monash University, a Graduate Certificate in Management (Technology Management) from Deakin University and is a member of the Australian Institute of Company Directors.

Mr Peter R E Turvey, Principal, Foursight Associates

Peter has worked in the life science sector for nearly 30 years; ten years with one of Australia's first biotechnology companies, Biotechnology Australia Pty Ltd, as Company Secretary. He was responsible for the protection of its intellectual property among other things. Peter spent 20 years with CSL Limited as its first in-house counsel and then as Company Secretary and Group General Counsel. As a member of the Executive Management Group, Peter was heavily involved in CSL's transformation from a government-owned enterprise to the global plasma and biopharmaceutical company it is today.

Peter is currently a Principal in the life sciences consultancy firm, Foursight Associates Pty Ltd, and a non-executive director of Starpharma Holdings Limited, AusBiotech Ltd, Allied Healthcare Group Ltd, Coridon Pty Ltd, and Agriculture Victoria Services Pty Ltd, a Victorian Government-owned enterprise.

FIFTEEN Appendices

Appendix 1

Schematic showing typical development pathway, specific to a bio-pharmaceutical

	0-2 years	2-4 years	4-6 years	6-8 years	8-10 years	10-12 years	12-14 years
Regulations	Patent Application	Clinical trials application			Regulatory Approval		Regulatory approval
Probability of success*			71% (71%)	44% (31.2%)	69% (21%)		
Trials	Basic Research/ Proof of Concept	Phase 0 Toxicology and animal testing	Phase 1 a & b Dosing trials	Phase 2 a & b Small cohort trials	Phase 3 Large cohort trials		Phase 4 Post-marketing studies
Product & Commercial Milestones					Prepare data package	Submit data package and apply for re-imbursement	Market Launch

*Probability of success for each phase (and cumulative totals in brackets). Note that probabilities will differ between disease groups and from biologics to small molecule medicines (Table 2.9 Di Masi's parameters for clinical trials, quoted in Ref 24.)

Appendix 2

Schematic showing typical development pathway, specific to a medical device²⁹

	0-1 years	1-2 years	2-4 years	4-5 years	5+ years
Regulations			Standards testing and technical file compilation	Regulatory Approval	
Trials	Phase 0 Analysis Proof of principle test beds (Unit testing)	Phase 1 Feasibility Concept demonstrator prototypes	Phase 2 Development (Detailed design and design Alpha and Beta prototypes - integration testing transfer)	Phase 3 Implementation Pilot production units (Product and process validation)	Phase 4 Monitoring Market launch & commence regulatory authority audits
Product & Commercial Milestones		Confirm feasibility	Design finalised		
	ISO 13485 compliant process				

Appendix 3

Schematic showing typical development pathway, specific to a genetically modified crop¹⁰

	0-2 years	2-4 years	4-6 years	6-8 years	8-10 years
Regulations	Patent Application	Trials Approval			Regulatory Approval
Trials	Basic Research/ Proof of Concept	Field Trials			
Product & Commercial Milestones		Product Development	Field Evaluation		Market Launch

DISCLAIMER

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