

# CODE OF BEST PRACTICE

for Reporting by Life Science Companies



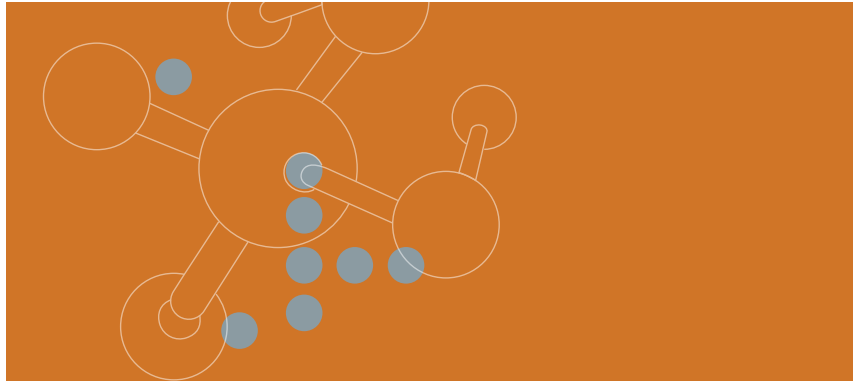
AusBiotech  
Australia's  
Biotechnology  
Organisation



ASX







## ONE / RATIONALE

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This Code has been jointly developed by ASX and AusBiotech following an extensive consultation phase involving key representatives of the Life Science sector and the investment community. It has been prepared taking into account international best practice.

ASX and AusBiotech strongly encourage companies 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 focus required of an organisation in gathering and analysing information to support the disclosure is in itself valuable.

The objectives of the Code are:

- To promote effective and informative communication by Life Science companies to enable investors to better assess a company's value and prospects.
- To reflect international best practice in reporting, and enhance the reputation, integrity and

credibility of the Australian Life Science sector.

- To serve as an educational tool for Life Science companies and investors.

Investors often have difficulty understanding the activities and appreciating the value of Life Science companies. Life Science companies have unique characteristics that can make conventional equity valuation models difficult to apply. Examples of these characteristics include the complexity of the science, long development lead times, significant ongoing capital requirements, regulatory hurdles and complex intellectual property issues.

The Code is designed to bridge this "information gap" by providing a disclosure framework that identifies the key drivers of value for Life Science companies and gives guidance to companies on the information investors need to make informed investment decisions.

It also emphasises the importance of appropriate terminology and context to announcements to help investors understand the commercial

significance of what is being reported.

The Code has an important part to play in Australia because of the relatively high level of participation of retail investors in the Life Sciences sector.

The Code is intended to encourage best practice in reporting, but it is not mandatory. Companies already have important disclosure obligations under ASX Listing Rules which are mandatory. The Code is intended to assist companies by providing a framework of issues to consider in meeting their obligations under Listing Rule 3.1 and so promotes clear and effective communication and more consistent reporting across the sector.

It is recognised that the sector is dynamic and that it is evolving. The Code needs to be regularly reviewed to ensure it retains relevance and is of value to Australian Life Science companies. ASX and AusBiotech propose to set up an interpretation and review committee that will undertake this role.



## TWO / THE CODE AND ASX LISTING RULE DISCLOSURE OBLIGATIONS

### **Listing Rule 3.1**

Listing Rule 3.1 requires listed companies to immediately disclose information to the market that is likely to have a material effect on the price or value of their securities. It is the cornerstone of ASX's continuous disclosure framework and is regarded as central to the orderly conduct and integrity of the ASX market. The rule is given legislative support by section 674 of the Corporations Act, which imposes statutory liability for its breach in certain circumstances.

The footnote to the rule provides examples of information that might be required to be disclosed under the rule, if material.

Guidance Note 8 to the Listing Rules provides guidance on compliance with Listing Rule 3.1. It contains important information on the principles underlying the rule and the expected approach to its interpretation. This includes a requirement that it not be interpreted by companies in a restrictive or legalistic fashion, and an expectation that companies will comply with it "as interpreted in a way that best promotes" the principle upon which the Listing Rule is based.

The purpose of the rule is to elicit disclosure of the highest quality which is of benefit to the market.

### **How does the Code interact with the Listing Rules?**

The Code does not replace or modify any of the disclosure obligations imposed by Listing Rule 3.1. Listing Rule 3.1 is the primary disclosure obligation to be discharged by listed companies subject to the test of materiality and the exceptions specified by the rule.

The Code is designed to assist listed companies to adopt reporting practices that provide investors and the market with full and accurate information on their activities. The Code complements Listing Rule 3.1 in the following ways:

- It recognises the particular activities, issues, and events that might give rise to disclosure obligations for companies in the Life Sciences sector, and provides guidance to companies on circumstances in which disclosure obligations might apply.
- It provides guidance to companies on the detailed information expected to be disclosed in

circumstances where disclosure is required.

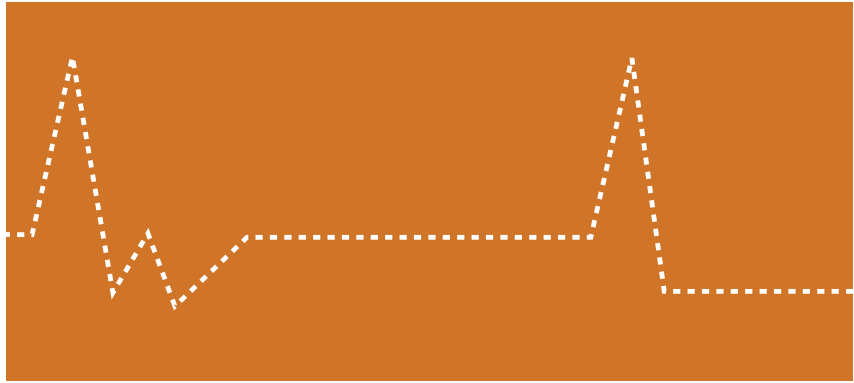
### **The materiality test**

The obligation to disclose is subject to a test of materiality. Companies are required to disclose information if a reasonable person would expect the information to have a material effect on the price or value of their securities. The converse applies in that companies are not required to disclose information that is not material.

The language of the obligation to disclose is similar to the language used in the Corporations Act. Guidance Note 8 provides guidance on the interpretation of the obligation with reference to sections of the Corporations Act, specifically sections 674 and 677.

### **Exception to the obligation to disclose**

Listing Rule 3.1A sets out an exception to the requirement to make immediate disclosure of material information. The intention of the exception is to protect the legitimate commercial interests of companies and their shareholders by not requiring immediate disclosure in certain restricted circumstances.



The exception operates by providing that where all three elements defined in the exception are satisfied, the primary obligation in Listing Rule 3.1 does not apply to the particular information.

The three elements are:

1. A reasonable person would not expect the information to be disclosed.
2. The information is confidential and ASX has not formed the view that the information has ceased to be confidential.
3. One or more of the following applies.
  - It would be a breach of a law to disclose the information.
  - The information concerns an incomplete proposal or negotiation.
  - The information comprises matters of supposition or is insufficiently definite to warrant disclosure.
  - The information is generated for the internal management purposes of the entity.

- The information is a trade secret.

The exception operates only while all three requirements are satisfied. If one or more of the requirements ceases to be satisfied, the exception no longer applies and the entity must disclose the information immediately. There may be circumstances where the three requirements of the rule appear to be satisfied, but ASX considers there is or is likely to be a false market in the entity's securities. In this case, ASX may ask the company to disclose the information or part of it, or to make a clarifying statement to the market.

There is a common misconception that confidentiality in itself provides an exception to the obligation to disclose. Listing Rule 3.1 sets out a number of tests, including confidentiality, all of which need to be met for the exception to apply.

#### **Companies involved in joint ventures**

Disclosure issues arise for companies in joint venture arrangements with other companies that face different disclosure obligations in particular

situations, either because different levels of materiality apply to the relevant information, or because disclosure requirements of the jurisdictions in which they operate are different.

These issues arise for listed companies across the board and need to be addressed in the context of the requirements of Listing Rule 3.1. ASX encourages companies to discuss disclosure issues with it in order to facilitate broad access to market information of the highest quality.

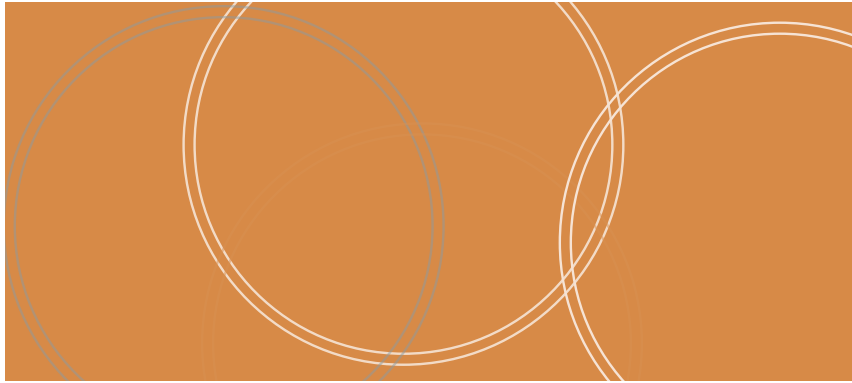
#### **The importance of maintaining confidentiality**

Meeting the Continuous Disclosure requirements raises particular issues for companies in the Life Sciences sector given the nature of their activities and the breadth of involvement of external parties in those activities. Companies should pay particular attention to the issue of confidentiality and the need to have systems and procedures in place to maintain confidentiality of information that would otherwise not need to be released to the market under Listing Rule 3.1A.

Where Listing Rule 3.1 requires that information is released, companies should be aware of the importance of ensuring that the information is not released to outside parties until they have received acknowledgment from ASX that it has released the information to the market. (Note the requirements of Listing Rule 15.7).

**Note** The advice contained in this section represents a summary only of the important features of Listing Rule 3.1. It is important that companies develop a full understanding of their obligations under the Listing Rules by referring to the rules themselves and the associated Guidance Notes. For further information, see <http://www.asx.com.au/supervision/rules/listing/index.htm>

Companies are also encouraged to raise and discuss any potential disclosure issues with their assigned ASX Issuers Adviser.



## THREE / SCOPE OF THE CODE

In developing the Code a very broad view has been taken of the definition of the Life Science sector. The Code is intended to include companies whose principal activities are in biotechnology, medical devices, and agricultural sciences.

The Code is not a “one size fits all” set of prescriptions. It recognises there is a broad range of companies in the Life Sciences sector representing significantly different sub-sectors as well as variations in size and activities. The Code contains guidelines and suggested practices that may not be relevant to all companies in all circumstances. It also recognises that information that may be required to be disclosed by one company under Listing Rule 3.1 may not be required to be disclosed by another because it is not material to the circumstances of that company.

## FOUR / THE CODE

The approach taken has been to focus on those aspects of Life Science companies that are key drivers of value. The sections that follow identify these drivers and outline appropriate disclosure practices relevant to them.

### 4.1 Intellectual Property Rights including Patents

#### Background

Intellectual property rights are an important consideration in the valuation of Life Science companies. They cover a range of exclusivity mechanisms, including:

- patents
- proprietary processes, procedures and information
- trade names
- trade marks; and
- market exclusivity

All of these have disclosure implications for Life Science companies, the strength of protection or exclusivity they provide being an important consideration in valuation. This section, however, deals primarily with patents as these are the most

relevant form of intellectual property for this sector.

Companies need to consider carefully the triggers for disclosure of patent information in their particular circumstances, and the extent of disclosure required. Disclosure requirements for mature companies with extensive and well-established patent portfolios will differ from those of less mature companies for which details of individual patents are of much greater significance.

#### What should be disclosed?

The basic principle is that all matters pertaining to patents, if material, should be disclosed on a continuous basis, with updates provided on a periodic basis. Companies should also explain the commercial significance of the information they disclose. A clear and comprehensive explanation will assist investors to understand the value of the intellectual property.

As a guide, the information disclosed at the first grant of a patent or patent family should include:

- the title of the patent
- a basic description of the subject matter covered by the patent
- the PCT Number (if applicable)

- the priority date
- the expiry date
- the status in key jurisdictions
- the patent number in key jurisdictions
- the filing date, and
- the identity of owner(s) if the company is not the owner, and the rights to the patent have been in-licensed

The fact that a patent application has been made is not usually material, but if this information is disclosed, communication to the market should be balanced and informative. Information regarding the existence of a patent application without providing the detail of the application, including its claims, is more likely to lead to an uninformed market than an informed one. It is also important to state clearly that there is a risk that a patent application will not be granted.

Particular care needs to be taken to ensure that investors are not given a misleading impression of the breadth of protection afforded by a patent. If material, significant opposition to patents, litigation relating to Intellectual Property, infringement claims and other actions or circumstances that restrict Freedom to Operate should be reported to the market.

#### Periodic updates of patent information

Companies should provide regular updates on the status of patents on at least an annual basis. To avoid unnecessary disclosure of detail, periodic updates can take the form of a concise table of summary

information that lists patents on a “patent family” basis, by status in the US, Europe, Australia and the rest of the world. The status should provide the relevant Patent/Application number, the PCT Number (if applicable), and indicate whether the patent is granted, pending or provisional.

The annual update is best included in the company’s annual report. If the statement is lengthy the company may choose to supply the information in an annexure or supplement. Display of the summary information on the company’s website is also considered good practice.

## 4.2 Licensing and other relationships of commercial significance

### Background

This section deals with licences and other relationships that can have a significant influence on valuation. The types of arrangements that may require disclosure under this section include:

- Material Transfer Agreements
- R&D Collaborations
- Licensing Agreements
- Supply Agreements
- Co-Marketing Agreements
- Joint Ventures
- Partnerships and Alliances

Companies must balance commercial sensitivity and the need to enable investors to properly assess the value of the transaction. There is often commercial sensitivity to the publication

of details of these agreements, and parties to transactions which do not have Listing Rule disclosure obligations may object to their disclosure. In these situations it is important that companies carefully evaluate their ability to withhold information in light of their obligations under Listing Rule 3.1. In particular, companies need to ensure that all three conditions set out in Listing Rule 3.1A are present for the exception to the disclosure obligation to apply. Confidentiality in itself is not sufficient for the exception to apply.

Companies should be conscious of the underlying principle that the ability of investors to value the company will be enhanced by full disclosure of information regarding value-driving transactions. However, the Code recognises the difficulties companies face in striking a balance between disclosure and the commercial interests of the company.

### What should be disclosed?

Companies should provide the market with information necessary to make a proper assessment of the significance of the transaction to the company<sup>1</sup>. In particular, companies should provide an explanation of the agreement to investors and give a clear indication of its commercial significance. Companies should also be careful not to mislead investors about the value and significance of the transaction. The risks associated with the transaction should be clearly explained.

Companies should provide a balanced view of the potential consideration to be derived from an agreement where precise details of the payment

<sup>1</sup> Public companies in the United States are required to file publicly material contracts to which they are a party. In the interests of comprehensive disclosure, companies may wish to consider this as a practice. However the importance of also providing clear guidance to the investor of the commercial significance of the transaction should not be overlooked.

provisions cannot be disclosed. For example, if a maximum total figure for potential consideration is given, companies need to be clear whether or not the receipt of payments is contingent on other elements of the transaction including performance measures or milestones. Companies should avoid giving prominence to potential revenue without also giving prominence to the conditions applying to the receipt of revenue and the timeframes in which the revenue can be earned.

As a guide, companies should consider providing the following information (where applicable) in reporting transactions of commercial significance including in-licensing and out-licensing arrangements:

- the names of the organisations that are signatories to the transaction, their locations and their website addresses;
- the nature and general use that may be made of the subject matter by the licensee (research, development, commercialisation);
- financial arrangements including licence fees, milestone payments, development costs and royalties and profit sharing. The range of royalty rates, or the minimum and maximum that the licensee will pay for the rights conveyed by the licence, and the event(s) that will trigger payments (fee upon signing, annual fee, percentage of net sales etc). If royalty rates are disclosed, then the basis of their calculation should be given as well, (e.g. paid as a percentage of net sales, or a percentage of total sales, or percentage of profits).
- whether only one party is obtaining rights (exclusive) or potentially many (non exclusive);
- a detailed description of the field covered by the transaction, including the disease indication

and the relevant territory (global, or specific country/ continent);

- the specific type of applications that may be made by the licensee (field of use to develop vaccines, diagnostic products, therapeutic products, human uses, veterinary uses);
- any conditions allowing the arrangement to be terminated, and details on the treatment of rights to Intellectual Property (and improvements on Intellectual Property during the period of the arrangement), following termination. e.g. reversion rights;
- responsibility of the respective parties to supply necessary resources and the nature of those resources e.g. responsibility for manufacturing and supply of commercial product;
- significant milestones and the respective obligations of the parties in reaching the milestones; and
- the ultimate impact of the transaction on the company's capital requirements. e.g. Will the company need to raise capital to fund its commitments under the transaction?

While out-licensing for research purposes is usually not a material event, companies should take care to disclose details of these transactions where they are material.

### 4.3 Regulatory matters including filings

#### Background

The development of a therapeutic product is a highly regulated process. There are likely to be a number of events and issues arising during a company's progression down the development path that will necessitate disclosure to the market.

To provide context to these potential disclosure requirements, this section

describes the typical regulatory and development path in some detail and provides guidance on likely disclosure events. The general principle is that companies should explain the regulatory process that applies to the development of products in the jurisdiction in which approval is being sought and report on significant steps in the development process as they occur.

#### What should be disclosed?

Companies developing pharmaceutical products in different territories are required to operate in accordance with the local regulations regarding the conduct of development and manufacture [in Australia, the regulatory authority is the Therapeutic Goods Administration (TGA), <http://www.tga.gov.au>]. Outcomes of applications for permits and certifications and other arrangements related to the ability to comply with regulations regarding the manufacture for clinical trials and for commercial products are likely to be material (see Section 4.8).

Generally, major changes in the development risks and costs are associated with specific regulatory decisions. Information on advances or delays along the development path is likely to be material. However, any announcements about regulatory and clinical development progress need to be factual; companies should avoid over-interpretation of the data prior to the review by the regulatory authorities, as the ultimate implications of the study are decided by the regulators.

Companies may also need to delay the release of detailed results and their implications until these are scrutinised by scientific professionals at conferences or published in journals. Premature releases may prevent such peer-reviewed presentations later, or could lead the financial markets to incorrect conclusions.

Companies should report significant steps in the reimbursement process

including reimbursement approvals and withdrawals involving both private and government payers.

### The US regulatory path

The specifics of the development hurdles and requirements for approval for marketing and sales may vary from product to product and from one country to another. Clinical trials conducted in Australia with unapproved drug products are regulated by TGA through the Clinical Trial Exemption (CTX) and Clinical Trial Notification (CTN) schemes (<http://www.tga.gov.au/docs/html/clintrials.htm>). The largest pharmaceutical market with the most publicly documented regulatory framework at present is in the US [US Food and Drug Administration (FDA), <http://www.fda.gov>]. Many Life Science companies therefore use the US regulatory path as the benchmark for their product development. The three major regulatory paths for drug product approval in US are explained in the footnote<sup>2</sup> below.

### Communications with regulators

The regulatory interactions with FDA take place through both structured and 'ad hoc' communications. The outcomes of some of these interactions can be material and may require disclosure. For example, FDA encourages the sponsor to make use of specified meetings with the agency at various stages of the development when major issues to do with the requirements of the agency for the

product approval are being dealt with. Companies should explain clearly the commercial significance of information relating to meetings with regulators.

### The typical regulatory path

The typical regulatory path in the US includes the following steps (for an interactive diagram, use the link <http://www.fda.gov/cder/handbook/develop.htm>):

#### Investigational New Drug (IND)

**filing Phase:** To initiate human clinical development in the US, it is necessary to file an Investigational New Drug application (IND) with FDA. The sponsor may choose to meet with 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.

Following IND application, FDA has 30 calendar days in which to decide if a clinical hold is necessary (i.e. if patients in the trial under the IND could be at an unacceptable risk). If 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 clinical hold is imposed, the sponsor must address satisfactorily the issues raised by 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.

**Phase 1:** "First in man" clinical trials may be purely exploratory in a new field of research, and their very conduct could therefore be commercially sensitive. Whether the companies should announce such studies will therefore often depend on how much further confirmatory work needs to be conducted for the "proof of concept". Once the company makes the decision to continue the development, the primary purpose of Phase 1 is to assess the initial safety of the product in humans, typically in a short trial in a small number of subjects (often in healthy volunteers).

**Phase 2:** These trials establish the safe and effective doses of the drug, typically in the target patient populations, using sufficient patient numbers and durations to provide reliable trends. They often act as a "rehearsal" for longer Phase 3 studies with more subjects.

The "end of Phase 2" meeting is one of the key meetings specified by FDA. The primary focus of this meeting is to determine whether it is safe to begin Phase 3 testing. This is also the time when protocols for Phase 3 human studies are discussed with FDA, and any additional information that may be required to support the submission of the new drug application (NDA) is identified. FDA and the sponsor also finalise the requirements regarding the manufacturing processes and their control, and the methods and

<sup>2</sup> A drug product approval in the US can essentially follow three paths: 1) A 505 (b)(1) New Drug Application (NDA) contains full reports of investigations of safety and effectiveness. 2) An NDA under 505(b)(2) contains full reports of investigations of safety and effectiveness, but where at least some of the information required for approval comes from studies not conducted by or for the applicant/sponsor, and for which the applicant has not obtained a right of reference. 3) An ANDA (abbreviated new drug application) that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product. Other special regulatory provisions include "orphan drug" designation for new treatment of rare disease. The nature of the regulatory designation is typically material as it is likely to affect the cost and duration of the product development as well as the period of exclusivity for the product on the US market. Other important regulatory classifications in the US are "Subpart E" and "Accelerated Development Review", introduced to expedite the development, evaluation, and marketing of therapies intended to treat people with life-threatening, serious and severely-debilitating illnesses, especially where no satisfactory alternatives exist.

specifications for testing the quality of the materials and the finished product. The outcomes of this meeting are likely to have a material impact on the company.

A sponsor can request FDA to review protocols regarding animal carcinogenicity studies, product stability and Phase 3 clinical trials under the Special Protocol Assessment (<http://www.fda.gov/cber/gdlns/protocol.pdf>). Reaching agreement with FDA on the design, execution and analyses in these protocols can have a significant effect on the product approval risk management at these stages of product development.

Regulatory inspections and approvals related to the manufacturing facilities for the product are dealt with in Section 4.8 of this Code; these take place in parallel and in conjunction with the NDA review.

**Phase 3:** the purpose of these clinical trials is to test the safety and efficacy or otherwise of the new treatment in the target patient population. Such studies require large numbers of patients – typically from hundreds to thousands – and treatment duration that reflects the intended use of the drug. Upon successful completion of Phase 3 studies, the sponsor meets with 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 NDA.

The FDA may use public meetings with the sponsor and advisory committees to obtain outside advice and opinions from expert advisers so that final agency decisions will have the benefit of wider expert

input. The advisory committees' recommendations, however, are not binding on FDA.

At the end of the review, 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 FDA to discuss these issues.

#### **Phase 4 or Postmarketing Studies:**

These are studies that are required of, or agreed to by, a sponsor, to be conducted after approval of the product for marketing by FDA. The requirements for such studies and the consequences of their outcomes could be material for the company.

## 4.4 Research and Development

### RESEARCH

#### **What should be disclosed?**

When releasing information on a product which is the subject of research, companies need to ensure that it is fair and accurate, and that it provides fair balance in presenting and addressing the prospects for the product.

### NON-CLINICAL<sup>3</sup> EFFICACY STUDIES

#### **Background**

Efficacy studies performed in vitro or in animals often constitute the only evidence from an early-stage company yet to enter a compound into clinical trials. This situation can persist for several years. Consequently non-clinical efficacy data, often as yet

unpublished, can be the only objective measure of the value of a company's technology in the early stages.

#### **What should be disclosed?**

Companies that wish to publicise the positive outcome of efficacy studies should provide sufficient summary information to enable a fair understanding of the result. Numbers of animals, negative and positive control groups, statistical significance and the relevance of the particular animal model under investigation are all factors which are needed to provide a fair understanding.

Companies should not selectively report positive results without reporting other relevant negative results.

### NON-CLINICAL SAFETY STUDIES

#### **Background**

Toxicology and safety pharmacology studies performed in vitro and in animals are designed to discover the potential dangers of a compound, often at very high doses of hundreds or thousands of times the anticipated maximum human dose. They are complex and are performed in several stages.

Expert interpretation is important in the assessment of the likely safety of the compound. In considering whether to permit a human trial, the regulator or ethics committee determines whether the preclinical safety package provided by the company justifies exposing humans to the drug.

#### **What should be disclosed?**

Companies should be careful about providing their own favourable assessment of a non-clinical safety package prior to confirmation by ethics or regulatory review of the data.

<sup>3</sup> For the purpose of this section "non-clinical studies" includes "preclinical studies". The use of this term recognises that studies of this kind can occur at various stages along the development path including the pre-clinical stage.

Where an assessment is made in these circumstances, companies should provide a caveat that the data is still subject to review by a relevant agency or ethics committee. Information should be provided to inform investors of the extent of toxicity testing and other safety studies performed, and a timeframe for completion of studies not yet performed.

When reporting on the results of a completed non-clinical safety study, companies should explain the implications for any future study, in particular, the type of clinical trial the study is intended to support eg. the duration and level of human dosing applicable.

## 4.5 Clinical Trials

### Background

The guidelines below are primarily suited to human therapeutic trials but the principles underlying them also have some relevance to medical device trials. Specific disclosure requirements for medical device clinical trials are dealt with in Section 4.6 of the Code. Much of this section is also not relevant to clinical trials of generics which have unique characteristics because of the regulatory process applying to them.

The progress of clinical trials and, in particular, the reported results of trials and their relevance to the disclosed endpoints represent an

important driver of market value for Life Science companies.

Companies should note recent international developments to promote greater transparency of clinical trial data. In March 2005, legislation was introduced to the US Congress requiring registration of clinical trials relating to prescription medicines<sup>4</sup>. Also, the pharmaceutical industry, represented worldwide by various industry associations, recently adopted a position on disclosure of clinical trial information by their member companies<sup>5</sup>. The importance of these developments is that it appears that Australian companies wishing to follow the regulatory path in the US and other major jurisdictions will be required to comply with these provisions.

### What should be disclosed?

Companies reporting on clinical trials should have regard to the general principles of disclosure suggested by the Code, in particular the need to disclose the goals, structure and protocol of the trial at the outset, and to disclose the results of trials as they relate to the original goals, structure and protocol.

It should be noted that where the term “drug” is used in these guidelines, it is intended to encompass a broader set of therapeutic products including, for example, gene therapy products or cell therapeutics.

### Clinical trials and how they relate to different regulatory paths

Companies should take care to ensure that any announcement relating to a clinical trial conveys the correct regulatory context of the trial. In particular, companies should ensure that any announcement regarding a clinical trial clearly states the way in which the study is linked to a relevant regulatory process. It is important that investors are not misled about the commercial or regulatory significance of a trial.

Companies should consider explaining the pathway to approval in their announcements and making it clear that achievement of endpoints does not necessarily lead to regulatory approval. Companies should be careful not to mislead the investor of the likelihood or timing of approval or the likely success of the product on the market following approval.

It is acknowledged that while some Phase 1 studies need to be disclosed, others do not. Some are exploratory e.g. relate to pharmacokinetics only, and lack material significance. Others, such as those that have an efficacy element in them, may need to be disclosed.

### Reporting at the Commencement of the Trial

The information announced at the commencement of the trial provides the market’s point of reference for assessing the reported results of the trial. It is important that the information clearly articulates the objectives of the trial and contains other relevant information

4 Among other things the proposed US legislation makes provision for the following:

- An accessible clinical trial registry and clinical trials results database
- Public availability of FDA internal drug approval and safety reviews
- Mandatory registration of all trials including foreign trials submitted to the FDA
- Prompt disclosure of the objectives, eligibility criteria, sources of funding and anticipated timelines of clinical trials
- Mandatory provision of clinical trial results

Companies should refer to <http://www.clinicaltrials.gov/> for more information.

5 *Joint Position on the disclosure of clinical trial information via clinical trial registries and databases* published by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA)

about the conduct of the trial. As a guide, it is expected that the following key information will be provided:

- **Name and any unique identifier of the trial:** e.g. Phase 2 trial on oral administration of drug X.
- **Primary endpoint(s):** The main purpose(s) of the trial. List of all the endpoints listed on the trial protocol as “primary endpoints”.
- **Secondary endpoints:** Companies may wish to disclose secondary endpoints listed on the trial protocol, but this is considered optional.
- **Blinding status:** Whether the trial is single blinded, double blinded or open label.
- **Product Development Status:** e.g. has it been made to GMP standards, is it made by a third party and is the third party expected to be the final commercial supplier of the approved product.
- **Treatment method, route, frequency, dose levels:** Basic design of the study including dosage levels, frequency, route (oral/IV etc), duration of treatment and follow-up, and any other key parameters of the trial design.
- **Number of trial subjects:** The number of trial subjects to participate, and in which dose group.
- **Description of Control Group:** Indication of size, control treatment and how and why the group will be chosen (e.g. randomised, historical etc.).
- **Subject selection criteria:** Key elements of the selection criteria for subjects to enter the trial, e.g. “healthy males aged 18-60”.

- **Trial locations:** The number of trial locations and the countries in which the trial will be conducted.
- **Partners:** Partners involved in the trial (if any).
- **Expected duration of the trial:** This should include an indication of when the trial is expected to start. It may require disclosure of matters that will affect the start, including the complexity of the trial protocol, the degree of preparation required, and the approvals required.
- **Additional information:** Other relevant information including factors that might affect the expected time frame (e.g. recruitment issues).
- **Trial standard:** The standard to which the trial will be conducted, e.g. ICH GCP.

The expected cost of the trial may also be material information that companies should consider disclosing.

#### Reporting during the Trial

Significant changes to a clinical trial program can have a considerable impact on market value and should be announced to the market. These may include a change to the endpoints of the trial, a significant delay in its progress, or an inability to recruit adequate numbers of patients affecting the statistical significance of the trial in meeting its endpoints.

Regular reporting of the progress of clinical trials including the recruitment process is encouraged but companies need to be careful not to give a misleading impression of the significance of events during the conduct of the trial.

#### Reporting Results

Reporting of results of clinical trials should be made regardless of whether the outcome is positive or negative, and should be clear and unambiguous, specifically addressing the endpoints announced at the commencement of the trial. There should be a clear statement regarding the implications of the trial results for the further development and potential sale of the product being tested. Companies should indicate whether a further clinical trial or trials is necessary or planned.

In meeting these requirements for disclosure, companies need to keep in mind the concerns of regulatory agencies regarding interpretation of results before they have been subjected to regulatory review. For example, companies need to be aware of the need to be consistent with FDA guidance for media releases.

The Code recognises the importance of peer review in the validation process and acknowledges that in some circumstances disclosure of results before peer review (through publication in a medical journal, presentation at a scientific meeting or otherwise) may be premature. Delay in disclosure raises particular Listing Rule issues, and companies need to be sure that the circumstances of any delay come within the terms of the exception to Listing Rule 3.1 contained in Listing Rule 3.1A.

It is expected that companies reporting results of clinical trials will provide the following information to the market. (Companies may consider it more informative to the market to provide a high level summary of the trial outcomes in the announcement, and include the detailed numerical results in tabular form in an appendix)<sup>6</sup>:

<sup>6</sup> There may be circumstances in which a market announcement is urgently required (for example, to correct or prevent a “false market” under Listing Rule 3.1B) but it is not possible, in the initial instance, to provide the level of detail expected by this section. In these circumstances it is important to clearly indicate the preliminary status of the announcement and to provide a timeframe in which the full information will be provided to the market.

- **Name and any unique identifier of the trial:** e.g. Phase 2 trial on oral administration of drug X.
- **Blinding status:** Whether the trial was single blinded, double blinded or open label.
- **Treatment method, route, frequency, dose levels:** Basic design of the study including for a pharmaceutical at least dosage levels, frequency, route (oral/IV etc), duration of treatment and any other key parameters of the trial design.
- **Number of trial subjects:** The number of trial subjects who participated, and in which dose group.
- **Dropout rate:** The number of trial subjects who dropped out in each dose group where the drop-outs occurred due to adverse clinical events related to the treatment or intervention.
- **Subject selection criteria:** Key elements of the selection criteria for subjects to enter the trial, e.g. “healthy males aged 18-60”. Demographics of those actually recruited also to be summarised, e.g. “the subjects ranged from ages 18 to 56.”
- **Control group:** Characteristics of the actual control group (e.g. demographics, disease severity) and how it compared to the treatment group before treatment.
- **Primary endpoint(s) results:**
  - Data on the outcome of all the primary endpoints set out in the trial protocol. Care should be taken to ensure that the report discloses data on the full set of primary endpoints. It is not expected that results in the form of raw data be provided.
  - The results of the primary analysis as prescribed in a statistical analysis plan devised before the lifting of the blind should be reported.
  - For a safety endpoint, a statement such as “the drug was safe and generally well tolerated” may be insufficient.
- For each pharmacodynamic primary endpoint, where relevant, the numerical and statistical results obtained for each dose group including placebo should be reported. At a minimum, dose group means and statistical significance (p-value or other relevant measure) compared to placebo of the relevant pharmacodynamic parameter should be provided, on the basis of:
  - (1) “intent to treat” – i.e. all subjects starting the trial, with missing values for non-completers treated according to LOCF (“last observation carried forward”) or other acceptable method; and
  - (2) “per protocol” – i.e. all subjects completing the trial according to the protocol.
- If analysis of a subgroup of the treated subjects (e.g. older, worse affected etc) was contemplated as part of the trial protocol, this may also be reported, but should not be provided in substitution of the analysis of all subjects.
- Any post-hoc analysis of the trial data relevant to the endpoints, such as post-hoc analysis based on subgroups of the trial subjects (e.g. “those more severely affected by the disease benefited most”) or post-hoc analysis based on measurements relevant to the primary endpoint but not part of the statistical analysis plan, may be reported but should be reported after the above analyses and clearly identified as post-hoc.
- It is common for the reported data to be preliminary in nature – i.e. obtained before inclusion in a final report. However if the reported data is preliminary, companies should still provide the information in the above format and report on all the primary endpoints in the report. Any subsequent substantive correction to preliminary data and results should also be reported.
- In the case of a blinded trial, the only other reports on the trial progress before the results report should relate to progress of recruitment and expected date of availability of results. Reports on data relating to the primary endpoints made before the blind is lifted may only be made in exceptional circumstances. In this regard, it should be noted that exceptional circumstances may exist where an obligation to disclose arises because the information has ceased to be confidential “in fact” as required by the exception (contained in Listing Rule 3.1A) to Listing Rule 3.1, or because ASX forms a view that a false market exists and asks the company to correct that false market in accordance with Listing Rule 3.1B.
- **Safety and tolerability:** Any findings relevant to safety and tolerability should be provided whether or not safety and tolerability is a primary endpoint. This should include information on adverse events which could be related to the product under trial, and the incidence rate relative to placebo and/or an active comparator.
- **Secondary endpoint(s) results:**
  - Data on the outcome of secondary endpoints set out in the trial protocol may be provided. If so, all requirements of reporting on the primary endpoints should also be adhered to in respect of the secondary endpoints.
  - If provided, the results of the secondary endpoint(s) should be reported after the primary endpoint(s).

## 4.6 Medical Devices

### Background

The medical device sector has points of differentiation that are relevant for disclosure under the Code.

A medical device is any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means.

The regulation of diagnostics is often coupled with the regulation of medical devices because many diagnostics “do not achieve their primary intended action, in or on the human body, by pharmacological, immunological or metabolic means”<sup>7</sup>. However, the term is also used for clinical or biological based tests which do not come within the medical devices regulatory framework. For this reason, this section does not specifically refer to diagnostics, although it is acknowledged that the same principles apply to relevant diagnostics.

A key area of differentiation of medical devices from the general Life Sciences sector is the stronger emphasis on engineering based research and development, and manufacturing.

The quality system within which the sector operates also differs from that which applies to other areas of Life Science. The quality environment covers activities from the design to manufacture, placing the product in the market and then subsequent post market vigilance. The quality system is audited throughout the device life cycle. Depending on the risk classification of the medical device, the device is also assessed in terms of safety and effectiveness.

Medical device companies are significantly represented in the Australian

Life Science sector yet the regulatory process for approval of their products is not well understood by the market. For this reason, this section focuses on the regulatory process in some detail. In explaining the regulatory process, the section concentrates on the US process as the US is the most commonly quoted of the regulatory bodies. There is a separate process for approval of medical devices in Europe. The European system is also based on risk classification.

There is an international effort to promote the convergence of medical device regulations amongst the established regulators and to encourage new regulatory jurisdictions to adopt these convergence guidelines (<http://www.ghtf.org>).

### Medical Device Classification and Regulation in the US

#### The US Jurisdiction

FDA's Centre for Devices and Radiological Health (CDRH) is responsible for regulating firms that manufacture, repackage, relabel, and/or import medical devices sold in the United States.

Medical devices are classified into Class I, II, and III classifications. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. A description of device classification and a link to the Product Classification Database can be found at: <http://www.fda.gov/cdrh/devadvice/313.html>.

#### Class I Devices – General Controls

Class I devices are subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than

Class II or Class III devices. Class I devices are subject to “General Controls” as are Class II and Class III devices.

Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments. Most Class I devices are exempt from the premarket notification and/or good manufacturing practices regulation.

#### Class II Devices – Special Controls

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. A few Class II devices are exempt from the premarket notification.

Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

#### Class III Devices - Premarket Approval

Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls.

Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

Premarket approval is the required process of scientific review to ensure the safety and effectiveness of Class III

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<sup>7</sup> See glossary

devices. Not all Class III devices require premarket approval to be marketed. Class III devices which are equivalent to devices legally marketed before May 28, 1976 may be marketed through the premarket notification [510(k)] process until FDA has published a requirement for manufacturers of that generic type of device to submit premarket approval data.

Examples of Class III devices which require a premarket approval include replacement heart valves, silicone gel-filled breast implants, and cerebellar stimulators, cochlear implants and artificial heart devices.

Class III devices which can be marketed with a premarket notification 510(k) are those postamendment (i.e., introduced to the U.S. market **after** May 28, 1976) Class III devices which are substantially equivalent to preamendment (i.e. introduced to the U.S. market **before** May 28, 1976) Class III devices and for which the regulation calling for the premarket approval application has not been published in 21 CFR. Examples of Class III devices which currently require a premarket notification include implantable pacemaker pulse generators and endosseous implants.

### Approval Process for Class III Devices:

#### Premarket Approval (PMA) - 21 CFR Part 814

Products requiring PMAs are Class III high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device. The PMA is an actual approval of the device by FDA. A description of the process and instructions for filing a PMA application can be found at: <http://www.fda.gov/cdrh/devadvice/pma/>

A well controlled Clinical Trial is required for a Class III device. Although

the implementation is different, similar principles of clinical trial design and evaluation are applied by other regulatory authorities.

#### Investigational Device Exemption (IDE) – 21 CFR Part 812

Clinical trials using unapproved medical devices on human subjects are performed under an Investigational Device Exemption (IDE). Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of nonsignificant risk must be approved by the IRB before the study can begin.

A description of the IDE process and information on FDA requirements for conducting a clinical study of an unapproved medical device can be found at <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>

#### Quality System Requirements

For a company to be able to supply medical devices to the market, the organisation must demonstrate that the device is designed, manufactured and marketed under a recognised quality system. The requirement for the quality system in the US is given by 21CFR Part 820. For high risk devices this system must be audited and approved prior to allowing the product to market, and is subsequently subject to regular audit.

#### What should be disclosed?

##### Quality System

A description of the quality system which the company operates should be disclosed in the Annual Report. This would include identification of major codes of compliance eg. ISO and FDA practices such as Good Manufacturing Practice.

Significant events in relation to the quality system, e.g. failure of a regulatory audit resulting in an inability

to sell into material markets should be considered for immediate disclosure.

#### Regulatory Approvals

Regulatory approvals that have a material impact on the value of the company should be disclosed to the market. For example, initial regulatory approval of a major new product into a major market would require disclosure, but approval of a small change to an existing product might not.

#### Clinical Trials

Clinical trials for devices are not typically described in the terms of Phases 1, 2 and 3 as they are for Pharmaceuticals. However, companies involved in clinical trials for devices should have regard to the principles of disclosure and reporting framework for clinical trials described in Section 4.5. Important among these is the need for disclosure of the goals, structure and protocol of the trial at commencement, and disclosure of results as they relate to the original goals, structure and protocol.

Reporting of clinical trial results will rest on materiality and will be influenced by such factors as the significance and stage of development of the product, as well as the size and stage of development of the company involved. Some device clinical trials will require detailed reporting (e.g. a trial of a new implantable device by an early stage company), while others may not (e.g. a trial of a modification to an existing device or a trial to permit entry into a small new market).

Clinical trials for devices may also differ from those relating to other Life Science products in that they may be more predictable in outcome owing to the level of testing possible prior to the commencement of the trial.

Where a company receives regulatory approval to market a device and the claims are agreed (usually on the basis of a clinical trial) this may have

a material effect on the value of the company and should be disclosed.

Clinical trial results that are not subject to approval by regulatory authorities should also be considered for disclosure.

## 4.7 Agricultural Biotechnology and Animal Health

### Background

The terminology used in the Code relates primarily to the pharmaceutical sector. Companies in other sectors of Life Sciences need to be aware of the similarities in their R&D and regulatory process to ensure that appropriate disclosure is made.

The Agricultural biotechnology and Animal Health sectors have different regulatory bodies controlling protocol, standards and certification. In Australia, the Australian Pesticides and Veterinary Medicine Authority (APVMA) sets the criteria and process for development products before they can be commercially promoted

The in-house R&D, including laboratory and field trials, conducted by companies within the Agricultural and Animal Health Life Science sector could be compared to the preclinical trials of pharmaceutical companies. A Product Development Agreement to demonstrate efficacy, for example, would therefore be equivalent to clinical trials in the pharmaceutical industry.

### What should be disclosed?

APVMA sets out specific requirements during and on completion of the regulatory process. Companies should disclose the meeting of these requirements.

Companies involved in development activities to achieve regulatory approval for the commercial sale of products should have regard to the principles

of disclosure and the reporting framework for clinical trials described in Section 4.5. Important among these is the need for disclosure of the goals, structure and protocol at the commencement of development activities and disclosure of the results of those activities as they relate to the original goals, structure and protocol.

Reporting of milestones and events along the development path will rest on materiality and will be influenced by such factors as the significance and stage of development of the product, as well as the size and stage of development of the company involved.

A Product Development Agreement in most cases would be considered material and should be disclosed. Approvals and compliance with food safety regulations may also be an important disclosure consideration for some companies.

## 4.8 Consultants' reports

### What should be disclosed?

When a company publicly releases a commissioned expert, patent, or technical report, it is important to disclose any payment made by the company to the expert in consideration for completion of the report. Payment includes payments in cash, equity, and debt instruments.

## 4.9 Manufacturing

### Background

Good Manufacturing Practice regulations (GMPs) are used internationally to ensure that producers of pharmaceuticals, medical devices and food products consistently manufacture to acceptable quality standards. GMP covers all production, from materials and premises to staff training and hygiene.

Many countries have formulated their own GMP standards, while others, for example ASEAN nations and the European Union, have harmonised their requirements. In the United States the US FDA (Food and Drug Administration) has made the GMP standard the minimum requirement, and called it cGMP, or current Good Manufacturing Practice, to highlight that it is a continual process.

This section does not specifically address the standards of countries other than Australia and the US. In many cases the standards are similar and accordingly the same principles of disclosure will apply.

The TGA (Therapeutic Goods Authority) in Australia is the key regulatory body for granting manufacturing compliance. GMP standards apply to all products, prescription and over-the-counter.

Product recalls, where a product is recalled from the market, are "voluntary" actions made by the firm. Although neither the TGA nor the FDA has the power to recall drugs, they can suggest action. Companies resisting such suggestions do so at their peril.

There are three classes of recall, with Class I being most serious. Usually there is a warning letter after an inspection of facilities, followed by the possibility of licence suspension or revocation if the inspection observations are not corrected. Seizures can also be made if there is an imminent risk to public health. The TGA or FDA can also take legal action if a company has repeatedly violated GMP requirements.

Consent decrees usually require companies, by consent, to fix the problems by certain dates and also pay various fines. Criminal charges can also be laid against an individual. Manufacturing under FDA accredited GMP standards is onerous. A number of US pharmaceutical companies have had

severe fines, shutdowns and product recalls due to failure to pass FDA audits.

It is worth noting that TGA does not currently require drug candidates to be manufactured under GMP conditions for Phase I trials. However any drug in Phase II development and beyond must use a drug manufactured to GMP standards.

#### **What should be disclosed?**

It is important for companies involved in manufacturing to set up quality control systems, and to ensure compliance with these systems once they are in place. Any deviations should be recorded and authorities alerted if the deviation is likely to affect the quality of the product. Where material these may require reporting to the market.

In Australia, TGA evaluates conformance with standards. FDA may also do so, if the product is to be sold in the US. The authorities conduct periodic inspections of facilities and test the products from the manufacturer, distributors or from retail stores.

During a regulatory audit, irregularities may be uncovered. It is a question of materiality whether these should be disclosed. Correcting minor irregularities is a part of running the business and should not be of any concern to investors. However a material irregularity that could adversely affect a company's performance should be reported, e.g. an irregularity that has the potential to result in a significant product recall.

If FDA conducts an inspection and grants a company a licence to manufacture for the US market this should also be disclosed if material. Conversely, the cancellation or significant alteration of a licence should be disclosed if material.

As a matter of course, companies should announce receipt of manufacturing approval from a regulatory body such as TGA or FDA.

## 4.10 Key staff appointments and departures

#### **What should be disclosed?**

Senior management and scientific staff are key agents for the achievement of the business goals of Life Science companies. Accordingly, in most cases the appointment or departure of executive staff reporting to the CEO or Board is a material event and should be disclosed to the market.

Responsibilities of such staff usually include Finance, Scientific Affairs, Clinical Affairs, Research and Development, Business Development, Regulatory Affairs and Licensing, Manufacturing, and Sales and Marketing. Additions to and departures from the Scientific Advisory Board may also be material information requiring disclosure. In any event, Listing Rule 3.16 requires the announcement of changes of chairperson, director, chief executive officer (or equivalent), or company secretary.

## 4.11 Periodic reporting of activities including product development

#### **What should be disclosed?**

Companies whose activities are primarily Research and Development are encouraged to provide periodic reports (at least half yearly) to the market providing details of their R&D activities in the preceding period, and a summary of expenditure incurred on those activities.

## 4.12 Financial reporting

#### **What should be disclosed?**

Information regarding cash flow and the extent of available cash balances is critical to the valuation of many Life Science companies. Companies

should consider providing commentary on cash flow, including implications for cash flow of significant activities such as Clinical Trials and changes in status of Clinical Trials. Many companies are in any event required to provide an Appendix 4C cash flow statement on a quarterly basis because of the requirements of Listing Rule 4.7B.

Other issues of relevance to investors that companies should consider disclosing on a periodic basis include:

- Information on sales volumes, especially in circumstances where marketing of the product is in the early stages
- A description of intangible assets included in the company's balance sheet
- Details of securities subject to escrow arrangements
- Any potential obligations to issue securities pursuant to licence agreements, e.g. obligation to issue securities on reaching predetermined milestones
- Transparent disclosure of share option arrangements

## 4.13 Terminology

Companies should be conscious that most investors will have very limited or no understanding of the science underlying the company's activities, and may have difficulty comprehending the company's announcements. It is important, therefore, to make announcements in terms that facilitate evaluation of the significance of the information being reported.

Many companies have addressed this need by providing comprehensive addenda and glossaries that explain general and company specific terms and concepts. Other ways include a Q&A section of the announcement dealing with issues that require explanation.



## FIVE / 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 it performs in the same manner as the original drug.

### **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.

### **cGMP**

Current Good Manufacturing Practice: The regulated manufacturing procedures required in the United States to ensure quality and purity of a drug compound during production

### **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 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.

### **Code**

Code of Best Practice of reporting by Australian Life Science companies, developed jointly by ASX and AusBiotech

### **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.

### **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 maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the procedure mandated by FDA, Phase 2 clinical trials gauge efficacy, and Phase 3 trials confirm it.

**FDA**

United States Food and Drug Administration - 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 etc.

**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 intellectual property rights of others. Prior to launching a new product or initiating a new line of research that may lead to the development of a new product, a process may be conducted to ensure ownership of the rights for all the components or constituents necessary to work the new product. Gaining these rights or permission is called "freedom to operate"

**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 Manufacturing Practice (GMP)**

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

**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 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.

**IND**

Investigational New Drug application, which is an application to 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.

**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 U.S. 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 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**

A compound 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.

**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
- 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.

### **NDA**

See New Drug Application

### **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.

### **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. There is little financial incentive for the pharmaceutical industry to develop medications for these diseases or conditions. Orphan drug status, however, 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  $\leq 0.05$  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.

### **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.

### **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 U.S. Patent Number XXXXXXX.” 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 chosen by the study sponsor. These experts review the trials for scientific merit, participant safety, and ethical considerations.

#### **Pharmacokinetics**

The activity or fate of drugs in the body over a period of time, including the absorption, distribution, localisation in tissues, biotransformation and excretion.

#### **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 to assess 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 effect**

A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

#### **PMA**

Pre-market Approval from the FDA to approve 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 (i.e. by chance) assigned to one of two or more treatment or placebo arms of a clinical trial.

#### **SAB**

Scientific Advisory Board

#### **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

#### **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.

#### **Statistical significance**

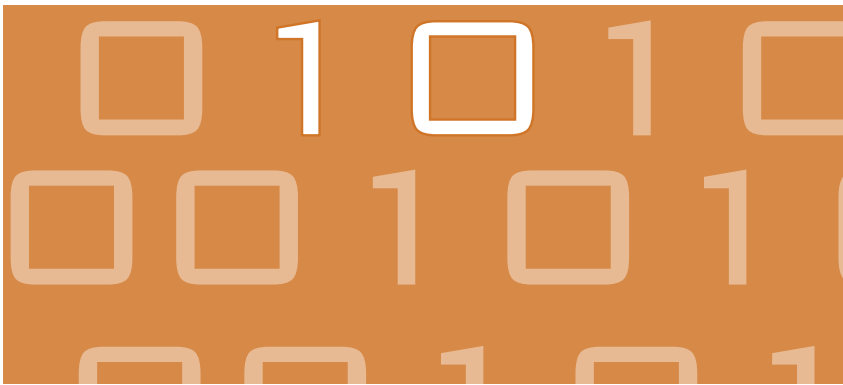
The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends among other things on the number of participants studied and the observations made, as well as the magnitude of differences observed.

#### **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.



## SIX / REFERENCES

- **UK BioIndustry Code of Best Practice;**  
<http://www.bioindustry.org/dbfiles/CGItemp29180.pdf>
- **Joint Position on the disclosure of clinical trial information via clinical trial registries and databases;**  
<http://www.phrma.org/publications/policy/admin/2005-01-06.1113.PDF>
- **Key disclosure issues for life science companies: FDA product approval, clinical trial results, and government inspections – An analysis of case law by William O. Fisher;**  
[http://www.mttl.org/voleight/FisherTYPE\\_HTML.htm](http://www.mttl.org/voleight/FisherTYPE_HTML.htm)
- **Clinical Trial Registration – A Statement from the International Committee of Medical Journal Editors,**  
<http://content.nejm.org/cgi/reprint/351/12/1250.pdf>
- **US Bill regarding disclosure of clinical trial results;**  
<http://www.govtrack.us/data/us/bills.text/108/s2933.pdf>
- **Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication;**  
<http://www.icmje.org/icmje.pdf>

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