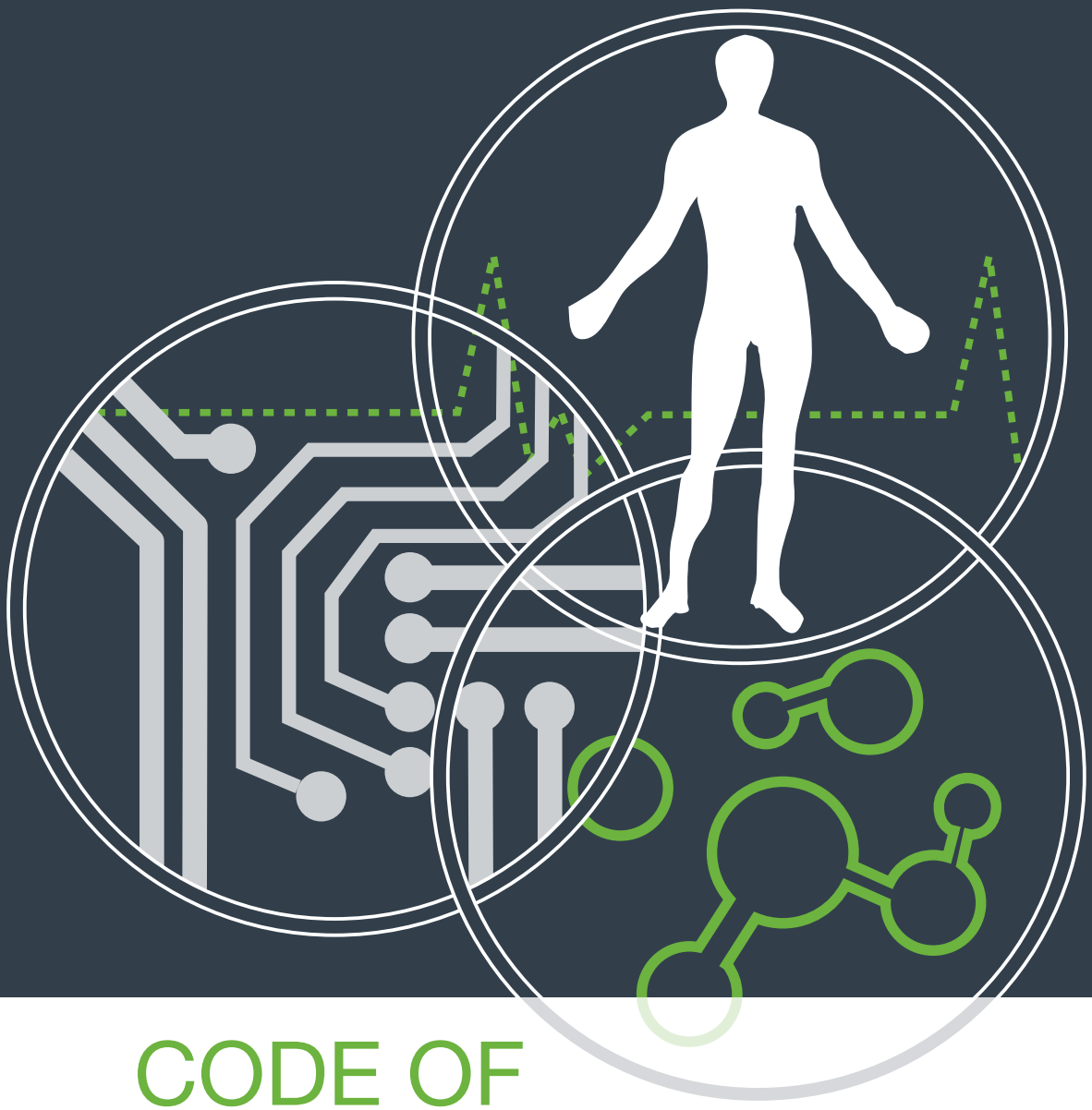


CODE OF BEST PRACTICE

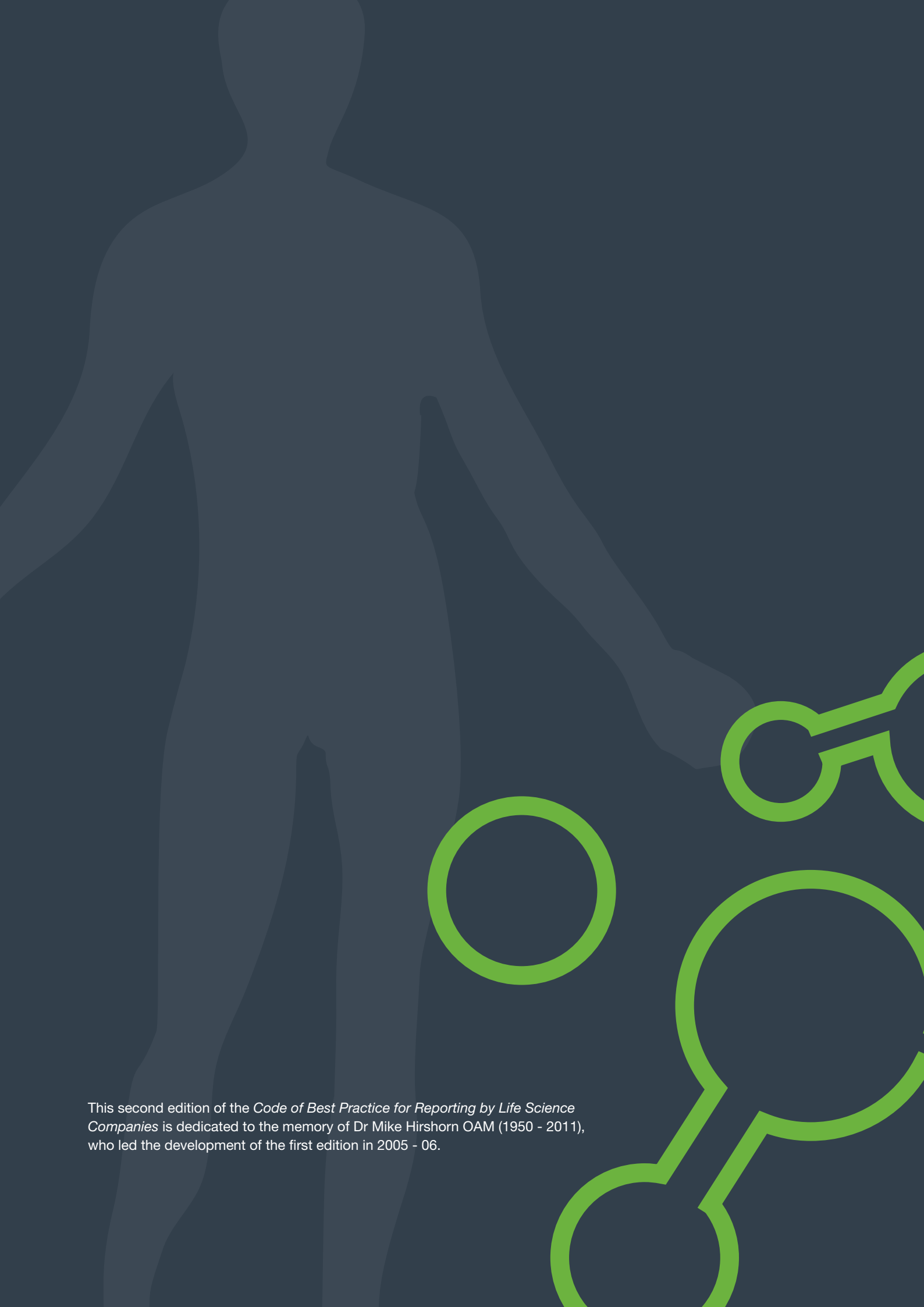
for Reporting by Life Science Companies

Second Edition

AusBiotech
AUSTRALIA'S BIOTECHNOLOGY ORGANISATION

ASX

State Government Victoria AUSTRALIA



This second edition of the *Code of Best Practice for Reporting by Life Science Companies* is dedicated to the memory of Dr Mike Hirshorn OAM (1950 - 2011), who led the development of the first edition in 2005 - 06.

CONTENTS

ONE RATIONALE

This Code was originally published in 2005 after extensive consultation with Australian Security Exchange (ASX), members of AusBiotech, other key representatives of the life science sector and the investment community (see list of contributors to the original document in Appendix 1).

This revision was undertaken in 2012-13 by a Reference Group (see list of membership in Appendix 2), to reflect current practice. The revision and update was supported by the Victorian Government.

ASX and AusBiotech strongly encourage companies in the life science sector 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 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 science sector that make communication with the market potentially challenging, hence prompting AusBiotech and the ASX to develop and review a Code specifically for this sector. Examples of these areas include the complexity of the science, long development lead times, significant ongoing capital requirements, regulatory hurdles and complex intellectual property issues.

The objectives of the Code are:

- To provide a reference tool to guide public Australian life science companies in effective and informative communication to the market, according to a guidance framework;
- To incorporate international best practice in reporting, and thus maintain and enhance the reputation, integrity and credibility of the Australian life science sector; and
- To provide information to investors about the disclosure framework that identifies the key drivers of value for life science companies, supporting more informed investment decisions.

The Code 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 science sector.

The Code is intended to be read in conjunction with ASX Listing Rule 3.1 to ensure that life science companies fulfill their obligations under that rule through providing clear and effective communication and consistent reporting across the sector.

TWO THE CODE AND ASX LISTING RULE DISCLOSURE OBLIGATIONS

Listing Rule 3.1

Listing Rule 3.1 requires listed companies to immediately disclose to the market any information concerning them that is likely to have a material effect on the price or value of their securities. The rule is given legislative support by section 674 of the *Corporations Act 2001*, which imposes statutory liability for its breach in certain circumstances.

Guidance Note 8 to the Listing Rules assists listed companies to understand and comply with their disclosure obligations. Substantially revised in 2013, it contains important information on the principles underlying the rule and the expected approach to its interpretation. This includes the obligation for companies to comply with the spirit, intention and purpose of Listing Rule 3.1 and to make disclosure which is accurate, complete and not misleading.

Whenever possible, an announcement under Listing Rule 3.1 should contain sufficient detail for investors to understand its ramifications and to assess its impact on the price or value of the company's securities.

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, which 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 science sector, and provides guidance to companies on circumstances in which disclosure obligations might apply;
- It provides guidance to companies on the level of detailed information expected to be disclosed in circumstances where disclosure is required; and
- It strengthens the clarity of disclosures by explanation of the terms typically used in material disclosure statements by life science companies.

The materiality test

The obligation to disclose is subject to a test of materiality as set out in section 677 of the *Corporations Act 2001*. Under that section a reasonable person is taken to expect information to have a material effect on the price or value of a company's securities if the information "would or would be likely to, influence persons who commonly invest in securities in deciding whether to acquire or dispose of" those securities. The converse applies in that companies are not required to disclose information that is not material.

Companies should carefully consider which information needs to be disclosed, since this can be different for each company. For example, disclosure requirements for mature companies with extensive and well-established operations will differ from those of less mature companies for which details of individual events are of much greater significance.

Exceptions to the obligation to disclose

Listing Rule 3.1A sets out exceptions to the requirement to make immediate disclosure of material information. The intention of these exceptions is to balance the legitimate commercial interests of companies and their shareholders

with the legitimate expectations of investors and regulators concerning the timely release of market sensitive information.

The exceptions operate by providing that where *all three* requirements are satisfied, the primary obligation in Listing Rule 3.1 does not apply to the particular information. Should any one of the three exceptions no longer be satisfied, information must then be disclosed immediately.

The three exceptions are:

1. One or more of the following five situations 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.
2. The information is confidential and ASX has not formed the view that the information has ceased to be confidential.
3. A reasonable person would not expect the information to be disclosed.

Disclosure issues specific to life science companies

Among the disclosure issues and scenarios addressed by Guidance Note 8, there are two that may be especially applicable to life science companies.

1. Commercially sensitive information - While a trade secret is protected from disclosure, some commercial information can't be so characterised and must be disclosed - such as a material contract for the marketing and sales of a patented drug. An announcement may legitimately avoid disclosing commercially sensitive matters provided it includes sufficient information to enable a proper assessment of the impact of the transaction on the price or value of the company's securities by disclosing the impact on revenues or profits, but not volumes to be delivered or unit prices.
2. Disclosure contrary to contractual commitments - Disclosure issues arise for companies that joint venture or contract 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. The ASX listing rules are contractually binding on a listed company and are enforceable against a company under both the Corporations Act and general law. So as to not allow a conflict between its disclosure obligations and its contractual commitments, a company that enters into a confidentiality or non-disclosure agreement should insist upon an express carve-out for the disclosure of information required by Section 674 and Listing Rule 3.1.

The importance of maintaining confidentiality and being able to respond to false markets

Meeting the continuous disclosure requirements raises particular issues for companies in the life science 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. For information to be confidential it will be known to only a limited number of people, secondly those people understand it is to be treated in confidence and only used for permitted purposes, and lastly, they abide by that understanding. Guidance Note 8 suggests practical measures that can be applied to safeguard the confidentiality of price sensitive information.

Where a company is relying on listing rule 3.1A not to disclose information about a material transaction it is negotiating, ASX would strongly encourage it to monitor trading in its securities; the print, electronic and social media; and enquiries it receives, for signs that information about the transaction may no longer be confidential. A company must be capable of responding appropriately either with an immediate announcement or a request for a trading halt in the event of any leak.

False markets arise where material information, which is partly or wholly inaccurate, circulates about a company and a segment of the market trades on the basis of it. Examples include a credible news article that a company is about to enter into a material acquisition or a rumour that a company is in serious financial difficulties. If ASX is concerned that there is, or is likely to be a false market, a company must be ready to respond in a timely manner to correct or prevent the false market by making a disclosure to the market. If the company does not do so voluntarily, under Listing Rule 3.1B it may be required to by the ASX.

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, pharmaceuticals, 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 science 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.

Note that 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 www.asx.com.au/resources/listing_rules.htm

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

FOUR THE CODE

Technologies based on life science (biotechnologies) are rapidly evolving with a definite trend toward niche markets, as personalised medicine becomes a reality, stem cell therapies begin to deliver results and technologies converge. So too the landscape – regulation, laws, intellectual property legislation, etc. – is also changing.

The approach in this Code has been to focus on those general aspects of life science companies that are key drivers of value, which differ from considerations in non-life science companies. The sections that follow identify these drivers and outline appropriate disclosure practices relevant to them.

4.1 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 balance in presenting and addressing the commercial prospects for the product.

NON-CLINICAL EFFICACY STUDIES

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

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.

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, such as the duration and level of human dosing applicable. If the studies are conducted using the quality systems described as Good Laboratory Practice (GLP), this may be also included in the disclosure, as GLP is typically required for pivotal animal safety studies.

4.2 Clinical trials

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 4.7 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 requirements for registration of clinical trials relating to prescription medicines. The pharmaceutical industry, represented worldwide by various industry associations, have a published position on disclosure of clinical trial information by their member companies.[1] Essentially, all confirmatory clinical trials and all exploratory efficacy trials at a minimum should be submitted for listing on any one of a number of free, publicly accessible, internet-based registries no later than 21 days after the initiation of patient enrollment, without prejudice to national legal requirements. The registries include the National Library of Medicine in the US (www.clinicaltrials.gov), the UK Current Controlled Trials (www.controlled-trials.com) and the Japan Pharmaceutical Information Center (www.clinicaltrials.jp), regardless of where the trial is physically conducted.

Australian companies wishing to follow the regulatory path in the US and other major jurisdictions are 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 key aspects of the 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, biologics (proteins, peptides, antibodies, vaccines, gene therapy products, etc.) 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 may lack material significance for the company, especially if that company has other programs in late-stage development. 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 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 for the treatment of disease Y;
- 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 status: This is especially important for Phase 3 clinical trials. For example, has it been made to good manufacuring practice (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 subjects to be recruited, and in which dose group;
- Description of Control Group: Indication of number of subjects, the nature of the control treatment and how and why the group will be chosen (For example, 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;
- Name of the principal investigator.
- Partners: Partner organisations involved in the trial (if any);
- Expected duration: 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. good clinical practice (GCP).

The expected cost of the trial and the source of funding 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 as soon as possible after they are identified.

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 the US Food and Drug Administration (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):

- Name and any unique identifier of the trial: e.g. Phase 2 trial on oral administration of drug X for the treatment of disease Y;
- Blinding status: Whether the trial was single blinded, double blinded or open label;
- Treatment method, route, frequency and 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 subjects who participated, and in which dose group.
- Dropout rate: The number of trial subjects who dropped out in each dose group where the dropouts occurred due to adverse clinical events related to the treatment or intervention;
- Subject demographics: Demographics of those actually recruited 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 would 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 end points 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).

4.3 Regulatory and reimbursement matters

The development of a life science-based product is usually 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, development and reimbursement path and provides guidance on likely disclosure events. The general principle is that companies should explain the relevant regulatory impacts and reimbursement options and impacts, which apply to the development and sale of products in the jurisdiction in which approval is being sought and report on significant steps as they occur.

What should be disclosed?

Companies developing products in different countries are required to operate in accordance with the local regulations regarding the conduct of development and manufacture. 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 4.6).

Bodies which are financially responsible for the costs of healthcare (public health authorities and private providers) may provide reimbursements, which in some cases can be as critical as market regulators. Although such payers do not determine whether a product may be lawfully marketed, payers' policies can determine which products are successful in the marketplace and which are not. For example, a decision by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) recommendation to list or not list on the Pharmaceutical Benefits Scheme is material.

Generally, major changes in the path to market incur different risks and costs depending upon specific regulatory and reimbursement decisions. Information on advances or delays along the 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 and reimbursement authorities, as the ultimate implications are decided by the regulators and payers.

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 regulatory and reimbursement process, including reimbursement approvals and withdrawals involving both private and government payers.

THE REGULATORY PATH

The specifics of the development hurdles and requirements for approval for marketing and sales will vary from product to product within life science sub-sectors, and from sub-sector to sub-sector (e.g. agricultural biotechnology versus medical devices) and from one country to another. In Australia, the regulatory authorities include, for:

- 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/docs/html/clintrials.htm).

The largest pharmaceutical market with the most publicly documented regulatory framework at present is in the US, the FDA (see www.fda.gov). Many Australian life science companies therefore use the US regulatory path as the benchmark for their product development. The FDA also regulates medical devices, food additives, vaccines, biologics, veterinary products and more, each with different regulatory requirements, processes and inflexion points that may be material.

Regulatory approvals for product and clinical trials in the European Union are conducted in accordance with the European Medicines Authority (EMA) regulatory guidelines (see www.emea.europa.eu/ema). A marketing authorisation from a regulatory body in a member state is required before a human therapeutic product can be marketed in Europe.

Communications with regulators

Interactions with the appropriate regulator 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, the 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 appropriately explain the commercial significance of information relating to meetings with regulators. For example, requirements for longer or additional studies, changes, in the study design and primary endpoints may materially impact the cost and duration of the development, the change in risk factors and size of the potential market.

The typical regulatory path of a medicine in the US

The typical regulatory path in the US includes the following steps (see www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm for more information):

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 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.

Equivalent filings for diagnostics and animal health applications are Investigational Device Exemption (IDE) and Investigational New Animal Drug (INAD) respectively.

Following lodgment of an IND application, the 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 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 clinical 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.

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 or not 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 and tolerability 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.

The "end of Phase 2" meeting 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 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 include "orphan drug" designation for new treatment of rare disease, "Subpart E" and "Accelerated Development Review" which are intended to expedite review of therapies to treat life-threatening or seriously debilitating diseases, especially where no satisfactory option exists. A "Breakthrough Therapy Designation" is also available. For a biologic, the equivalent to an NDA is a Biologics License Application (BLA). Regulatory designation is often material as it is likely to affect the cost and duration of the product's development as well as the period of exclusivity on the US market.]

The equivalent FDA filings for diagnostics and devices are Pre-Marketing Approval (PMA) for novel devices, 510(k) for devices where a comparison can be made with a predicate device, de-novo 510(k) for lower risk predicate-free devices and 510(k) exempt for low risk devices. Humanitarian Device Exemption (HDE) designation is approximately equivalent to orphan status for human drugs.

In animal health the equivalent 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 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. The outcomes of this meeting are likely to have a material impact on the company.

A sponsor can request the FDA to review protocols regarding animal carcinogenicity studies, product stability and Phase 3 clinical trials under the Special Protocol Assessment[2]. 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, and may be a material event.

Regulatory inspections and approvals related to the manufacturing facilities for the product are dealt with in Section 4.6 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 typically require larger numbers of patients and treatment duration that reflects the intended use of the drug. Upon successful completion of Phase 3 studies, 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.

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 the FDA.

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. These communications with the FDA are likely to have a significant material impact.

Phase 4 or post-marketing studies: These are studies that are sometimes required of, or agreed to by, a sponsor, to be conducted after approval of the product for marketing by the regulator. The requirements for such studies and the consequences of their outcomes could be material for the company.

THE REIMBURSEMENT PATH

Depending on the country in which a healthcare product is to be sold and the biotechnology sub-sector, opportunities for reimbursement (access to payers) will differ substantially and a listing on a formulary or scheme (or in some cases exclusion from it) may be material.

Reimbursements 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), an insurance plan (public or private), or by governments.

Public plans may be structured in a variety of ways, including:

1. Universal, as in Australia's Pharmaceutical Benefits Scheme;
2. Restricted by age, as in the Ontario Drug Benefit Plan for seniors;
3. Segmented by disease group, such as Manitoba's cystic fibrosis drug plan;
4. Aimed at supporting specific employee types, such as Veterans' Affairs for US ex-military personnel;
5. Geared to income, such as US Medicaid programs in many states;
6. 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 pharmaco-economics. 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 UK'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 their administrators), or hospitals may have their own review committees to advise which medicines to fund from a hospital's budget.[3]

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.[4]

Co-dependent technology

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 program 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.[5]

Pharmaceutical Benefits Scheme

In Australia, the majority of pharmaceuticals are reimbursed under the Pharmaceutical Benefits Scheme (PBS), which is administered by Medicare Australia. Listings are made on the recommendation of the Australian PBAC. The PBS provides a list of marketed medicines that are subsidised by the Commonwealth 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 per cent of prescriptions.

PBAC decisions are not binding and Ministerial approval (and in some cases Cabinet approval) is also required, however, a PBAC recommendation for listing is likely to be material.

At times post-marketing studies are conducted by sponsors seeking alternative reimbursement indications on the PBS, which may also be material.

Medical Benefits Schedule

Reimbursement is available in Australia for medical procedures, including those involving medical devices and diagnostics, via the Medical Benefits Schedule, which is administered by Medicare Australia on the recommendations of the MSAC.[6]

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 a MBS benefit is payable for the associated professional service. The PLAC review 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.[7]

In other parts of the world

Opportunities for reimbursement vary dramatically from country to country. The reimbursement system in the US, for example, is far more fragmented comparative 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 provided at federal (Medicare, Department of Defense, Biotechnology Industry Association) and state levels (Medicaid) to statutorily defined populations (elderly, poor, disabled, veterans, etc.). Many private insurers also cover Medicare and Medicaid populations financed by the government.[8]

Other players and intermediaries also exist in the payment systems such as preferred provider organisations, health management organisations, managed care organizations, etc. Approvals or inclusion by these bodies can also influence reimbursement success.

4.4 Intellectual property and regulatory exclusivity rights

Background

Intellectual property (IP) and regulatory exclusivity rights are an important consideration in the valuation of life science companies. They cover a range of exclusive rights, including:

- Patents;
- Proprietary processes, procedures and information;
- Trade names and international non-proprietary names;
- Trade marks; and
- Regulatory exclusivity.

These rights provide a company with a type of exclusivity (i.e., a period of time in which competitors are prevented from using the company's IP or data). Companies need to consider reporting on anything that may affect these rights.

Some of the more commonly used forms of rights in this sector are patents, trade secrets and regulatory exclusivity, as discussed below.

- **Patents** are useful for providing a company with the right to prevent others from using their technology.
- **Trade secrets** are useful for protecting information such as proprietary manufacturing or discovery processes, which can be difficult to protect by patent.

- **Regulatory exclusivity** is tied to approval of a product (e.g., drug, medical device or veterinary product) and may come in a number or 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) are:
  - » Data exclusivity;
  - » Marketing exclusivity; and
  - » Orphan drug status.

It is important to note that none of the above rights necessarily provide a company the right to actually use their technology without infringing another company's IP or regulatory exclusivity rights.

What should be disclosed?

The basic principle is that all matters pertaining to IP should be disclosed if they are likely to have a material effect on the price of securities (e.g., if they have a material effect on the ability of a company to maintain market exclusivity) and they are unlikely to be prejudicial to the company. Chapter 3 of the Listing Rules and Guidance Note 8 provide an explanation of general information that need not be disclosed. If a company elects to disclose information, it should also explain the commercial significance of that information. A clear and comprehensive explanation will assist investors to understand the value of the IP.

Examples of information that companies should consider disclosing include:

Patents

The level of disclosure in relation to patents may vary from company to company. For example, if a company's major market is the US, after grant of a US patent the company may disclose the fact that the patent has been granted, the patent number, the expiry date and a brief discussion of the subject matter claimed and how it relates to the company's commercial activities.

Companies may also consider reporting grant of a patent term extension, since this will confer an additional period of exclusivity protecting a commercial product.

The fact that a patent application has been filed is seldom material, it is generally only after grant that a patent right becomes a material asset, which should be disclosed. If information relating to patent filings or progress on patent applications is made, however, communication to the market should be balanced and informative. 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, the likelihood of grant of a patent or the ability of the company to enforce its patent rights.

Trade secrets

Obviously, companies cannot disclose their confidential information in reports to the market. However, they should consider disclosing if there has been a loss of confidentiality in any of their trade secrets, particularly for important or essential technologies, or if they have commenced litigation to prevent or gain re-imbursement for theft of trade secrets.

Regulatory exclusivity

Companies should consider disclosing any events that result in gain or loss of regulatory exclusivity. Such events could be approval of a new product by a regulatory body, approval of a new indication for a drug, approval of orphan drug status, expiry of market/data exclusivity or successful challenge to orphan drug status. Regulatory exclusivities vary from country to country and care should be taken when reporting on the extent of the right and period of exclusivity conferred.

Adverse actions

If material, challenges to a company's IP rights (e.g., by opposition or re-examination of patents), challenges a company makes to a competitors IP rights, and publicly available information regarding litigation such as infringement claims should be reported to the market. Similarly, resolution of challenges or litigation may also be reported. Of course, the materiality of any information must be considered on a case-by-case basis. For large companies involved in many oppositions on a regular basis, it may not be material that they have commenced a new opposition. However, for a small company built on single technology, a challenge to a patent covering that technology may be material.

4.5 Licensing and other relationships of commercial significance

This section deals with licensing 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. As discussed in Section 2 of the Code, in these situations it is important that companies carefully evaluate their obligations under Listing Rule 3.1.

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.

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 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 revenuecan 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. For example, will the company need to raise capital to fund its commitments under the transaction?

While out-licensing for research purposes is not usually a material event, companies should take care not to be constrained by confidentiality or non-disclosure agreements that would conflict with any Listing Rule 3.1 obligation that may arise (see section 2, regarding 'Disclosure issues specific to life science companies').

4.6 Manufacturing

GMP regulations 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 US the FDA has made the GMP standard the minimum requirement, and called it cGMP, or current GMP, 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.

Public companies in the US 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 practice. However the importance of also providing clear guidance to the investor as to the commercial significance of the transaction, should not be overlooked. NB: Such statutory filings are usually heavily redacted to remove commercial terms.

The TGA in Australia is the key regulatory body for granting manufacturing compliance. GMP standards apply to all therapeutic products, including prescription and over-the-counter medicines.

Product recalls, where a product is recalled from the market, are usually "voluntary" actions made by the company. Both the TGA and the FDA have the power to force the recalls under certain circumstances, however, they usually suggest action. Companies resisting such suggestions do so at their peril. Regardless of the circumstances, a product recall is likely to be material and therefore may require reporting.

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 license 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.

In the US, 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 be 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, the TGA evaluates conformance with standards. The 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 the 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 the TGA or the FDA.

4.7 Medical devices

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". 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 science 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. The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011 as a forum to discuss future directions in medical device regulatory

harmonisation. The voluntary group from Australia, Brazil, Canada, China, European Union, Japan and the US, as well as the World Health Organization (WHO) met in Ottawa to address the establishment and operation of this new Forum, built on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF). Progress toward international medical device regulatory harmonisation and convergence, is published at: www.imdrf.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, re-label, and/or import medical devices sold in the US.

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 pre-market approval. A description of device classifications and a link to the Product Classification Database can be found at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm2005371.htm

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 pre-market 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 post-market surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

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

Examples of Class III devices which require a pre-market 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 post-amendment (i.e. introduced to the US market after 28 May 1976) Class III devices which are substantially equivalent to pre-amendment (i.e. introduced to the US market before 28 May 1976) Class III devices and for which the regulation calling for the pre-market approval application has not been published in the Code of Federal Regulations Title 21 (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:

Pre-market 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: www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/default.htm#data

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 – 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 non-significant 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 www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm

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 GMP.

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 4.2. 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.

4.8 Agricultural biotechnology and animal health

The terminology used in the Code relates primarily to the pharmaceutical sector. Companies in other sectors of life science 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, www.apvma.gov.au) 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 sectors 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 4.2. 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 PDA 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.

4.9 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 board members, the chief executive officer (CEO), managing director, or in some cases senior executive staff reporting to the CEO or board, is likely to be 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, CEO (or equivalent), or company secretary.

4.10 Periodic reporting of activities including product development

What should be disclosed?
Companies whose activities are primarily R&D 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.

4.11 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. Most life science 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.

If companies become aware that their earnings for the current reporting period will differ materially from market expectations, they must also consider their listing rule 3.1 obligations to disclose the information immediately.

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; or
- Transparent disclosure of share option arrangements.

4.12 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 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 refer to exploratory, micro-dosing studies.

Code
The Code of Best Practice for reporting by 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.

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

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 against 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 trials confirm the efficacy and safety of the dose and frequency of dosing to be approved.

Food and Drug Administration (FDA)
The 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.

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;
- 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 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. These experts review the 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.

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)
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 (i.e. by chance) assigned to one of two or more treatment or placebo arms of a clinical trial.

Scientific Advisory Board (SAB)
An advisory board that gives guidance on 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 trials comparing the active ingredient vs 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.

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.

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SEVEN APPENDICES

Appendix 1

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The first edition of the Code was published in 2005, based on the contribution of the following people.

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Appendix 2

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A broad consultation was conducted in March 2013 and thanks are extended to the (17) companies and individuals who made submissions in response.

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ISBN 1 875262 41 5