

**Speculative**

See key risks on Pages 5 and 6 and Biotechnology Risk Warning on Page 9. Speculative securities may not be suitable for Retail Clients.

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# Paradigm Biopharmaceuticals (PAR)

## FY23 - Rich In New Data

**Recommendation**  
**Buy** (unchanged)  
**Price**  
**\$1.31**  
**Valuation**  
**\$2.20** (unchanged)  
**Risk**  
**Speculative**

**GICS Sector**  
**Pharmaceuticals & Biotechnology**

**Expected Return**

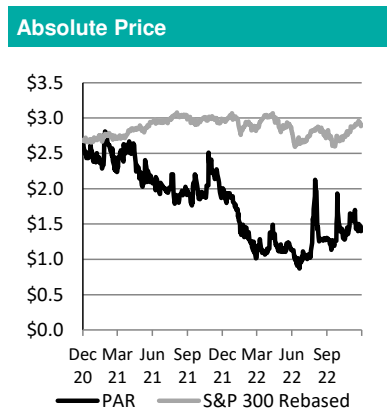
Capital growth	67.9%
Dividend yield	0.0%
Total expected return	67.9%

**Company Data & Ratios**

Enterprise value	\$274.8m
Market cap	\$366.8m
Issued capital	279.9m
Free float	92%
Avg. daily val. (52wk)	\$873,000
12 month price range	\$0.85 - \$2.15

**Price Performance**

	(1m)	(3m)	(12m)
Price (A\$)	1.39	1.29	1.94
Absolute (%)	1.08	9.34	-27.61
Rel market (%)	-2.84	4.32	-26.77



SOURCE: IRESS

### CY23 – Rich In Long Term Efficacy Data

Paradigm Biopharmaceuticals is well funded and in the midst of an extensive clinical program investigating the efficacy of its lead drug candidate Zilosul for the treatment of pain and the underlying disease in osteoarthritis (OA).

The company recently reported headline data from its synovial fluid biomarker trial (OA-008) with further data concerning 6 and 12 month efficacy expect to report in late 1Q CY23 and 2H23. Further evaluation on serum and urine biomarker correlations, and further longer-term clinical outcomes are in progress and are expected to report throughout the course of 2023.

By mid year we expect the final dosing regime for the phase 3 studies in OA will have been determined and recruitment to finally commence in 2H CY23. Once final dosing is determined, recruitment is expected to accelerate rapidly with dozens of sites expected to open within weeks of enrolment commencement.

### Ex Zilosul, treatment landscape remains bleak

The high unmet need for new drugs to treat osteoarthritis follows years of clinical trials investigating various biological agents to block inflammatory pathways all of which failed in clinical trials or had adverse safety profiles. Work has continued to investigate the role of Non steroid anti inflammatory drugs (NSAIDs) and corticosteroid injections for the long term relief of symptoms associated with OA. New data which emerged from the recent RSNA conference once and for all extinguishes any argument regarding the efficacy of NSAIDs as a long term treatment for the condition. Similarly for intra articular corticosteroids, data from recently published randomised trials found no evidence of long term pain relief from these therapies.

### Investment View: Retain Buy (Speculative) Valuation \$2.20

There are no changes to earnings. We retain our Buy (Speculative) rating and valuation of \$2.20. The company had \$92.3m in cash at 30 September and recently reported the receipt of \$7.4m R&D tax incentive refund.

**Earnings Forecast**

June Year End	FY22	FY23e	FY24e	FY25e
Revenues	0.1	0.0	64.5	62.2
EBITDA \$m	-39.4	-59.0	12.2	40.0
NPAT (underlying) \$m	-39.4	-58.5	12.7	40.5
NPAT (reported) \$m	-39.4	-58.5	12.7	40.5
EPS underlying (cps)	-16.9	-20.0	4.4	13.9
EPS growth %	na	na	na	2.2
PER (x)	nm	nm	30.1	9.5
FCF yield (%)	nm	nm	3.4	1089%
EV/EBITDA (x)	nm	nm	21.5	6.6
Dividend (cps)	-	-	-	-
Franking	0%	0%	0%	0%
Yield %	0.0%	0.0%	0.0%	0.0%
ROE %	na	na	20.4%	39.8%

SOURCE: BELL POTTER SECURITIES ESTIMATES

# NSAIDs and IACs - no long term benefit

## Treatment Landscape For Osteoarthritis

Over the years, numerous developers have attempted to make a difference in the lives of patients suffering the debilitating effects of pain associated with OA. These include the use of Non Steroid Anti Inflammatory Drugs (NSAIDS) and corticosteroids. Not surprisingly neither drug class has any impact on disease modification and limited long term impact on pain.

Large pharma companies have conducted extensive clinical trials investigating the potential of anti IL1 and anti TNF biologics with the aim of blocking pro-inflammatory pathways. These studies found no significant difference in function and pain with considerable adverse side effects.

In the following section we highlight two more recent studies which largely serve to re-confirm that which has been long suspected in relation to NSAIDs and Corticosteroid Injections in addition to shedding new light on the potential for disease acceleration.

### NON STEROID ANTI INFLAMMATORY DRUGS

Non Steroid Anti-inflammatory drugs including the likes of naproxen and ibuprofen are commonly prescribed for osteoarthritis pain and inflammation, however, there is no data regarding long term effects of these drugs on disease progression. In particular there is no data regarding the long term effects on synovitis – being inflammation of the membrane lining the knee joint.

The goal of this latest study was to analyse whether NSAID treatment influences the development or progression of synovitis and to investigate whether cartilage image biomarkers are impacted by NSAID treatment.

The patient group included the following:

- 129 participants each with moderate to severe OA and sustained treatment with NSAID for at least one year; and
- The control group consisted of 592 participants who were not treated with NSAIDs.

All participants underwent MRI imaging at baseline and at 4 years with images scored for biomarkers of inflammation including cartilage thickness as a marker for evaluating disease progression.

Not surprisingly in our view, the results showed no long term benefit from NSAID use. Joint inflammation and cartilage control were worse at baseline in the group taking NSAID's compared to the control group, and worsened after four year follow up, however, these differences between the two groups did not reach statistical significance.

The lead investigator concluded, that there were no protective mechanisms from NSAIDs in reducing inflammation or slowing down progression of OA of the knee joint<sup>1</sup>.

The key limitation of the study is that it was not randomised and the period under therapy appears to range from 1 to 4 years. Nevertheless, the data is instructive and confirms that NSAIDs have no function in disease modification.

### INTRA ARTICULAR CORTICOSTEROID INJECTIONS

Intra-articular corticosteroid injections (IACs) have been used for decades in the management of symptomatic osteoarthritis of the knee and remain a common practice.

<sup>1</sup> Impact of Non steroidal anti inflammatory drugs on synovitis and the progression of osteoarthritis: data from osteoarthritis initiative. Abstract presented at RSNA 2022.

The pain relief from a steroid injection is thought to work by reducing inflammation within the arthritic knee. Substantial variability remains among providers with regard to the technique used to perform the procedure, including the site of the injection, the medications injected, and the level of sterility.

The success of steroid injections in relieving arthritic knee pain most often occurs in the short term – up to about 6 weeks. However, the efficacy of intra-articular corticosteroid injections varies within the published literature. The latest American Academy of Orthopaedic Surgeons clinical practice guideline does not support conclusive recommendations about the use of intra-articular corticosteroid injections for symptomatic knee osteoarthritis.

The study by *Zeng et al* further quantifies the extent of the potential safety issues involved with long term use of intra articular corticosteroids. The key points from the study were:

- The investigators examined the relationship of IAC use to radiographic osteoarthritis progression in the real world setting;
- The trial involved 148 patients treated with IAC's and 536 controls;
- 65 knees (21.7/100 person years) in the IAC cohort experienced worsening Kellgren Lawrence Scores – being an increase in grade >1, verses the control group where 90 knees (7.1/100 person years) experienced a worsening of the Kellgren Lawrence grade.

The investigators made the following key observations:

- IAC's may be associated with increased risk of OA disease progression with the risk increasing with continued use;
- Repeated use of IAC's led to larger cartilage volume loss compared to saline; and
- The initiation of IAC's and continued use may have a detrimental effect on knee OA progression.

We conclude that neither NSAIDs or IACs represent a viable, safe solution to relief from pain associated with moderate to mild OA. There is no data to suggest anything other than short term pain relief and no evidence of any disease modification of the underlying disease.

## Recap of PAR OA-008

For the purposes of completeness we include here a summary of the key points from the recent headline data from PAR008 concerning the use of iPPS (aka Zilosul) for the treatment of knee OA.

The headlines data was reported in October 2022. Detailed analysis will follow in 2023 and is expected to be presented at a major medical conference in conjunction with the release of a peer reviewed publication of the results.

The aim of OA-008 was to provide novel scientific evidence to test the hypothesis that iPPS acts locally in the knee joint of OA subjects as well as provide data on whether biomarker changes correlate with clinical outcome (WOMAC pain and function assessments). Further evaluation on serum and urine biomarker correlations, and further longer-term clinical outcomes are in progress.

OA-008 was a randomised, double blinded controlled study in 61 patients covering three dose cohorts. Of these, we expect the dose for the upcoming phase 3 trials will be PPS twice weekly at 2mg/kg for 6 weeks<sup>2</sup>.

<sup>2</sup> Being the cohort responsible for generating reductions in pain and improvements in function.

**PRIMARY ENDPOINT**

The Primary Endpoint for OA-008 was the change (reduction) from baseline at day 56 in one or more synovial fluid biomarkers. These biomarkers and the outcome achieved are summarised below:

**Table 1 - Synovial fluid biomarkers**

Measure	Outcome
Nerve Growth Factor (NGF)	Reduced
Tumour Necrosis Factor Alpha (TNF $\alpha$ )	Reduced
Interleukin (IL-6)	Reduced
Cartilage oligomeric matrix protein (COMP)	Reduced
Aggrecan (ARGS) fragment	Reduced
Tissue inhibitor matrix metalloproteinase 1 (TIMP-1)	Increased

SOURCE: COMPANY DATA

The direction of movement (Increased/Reduced) were in line with expectation. In all cases, the changes in synovial fluid biomarkers at day 56 were favourable compared to placebo controls. The detailed data has been held back in anticipation of a future peer reviewed journal.

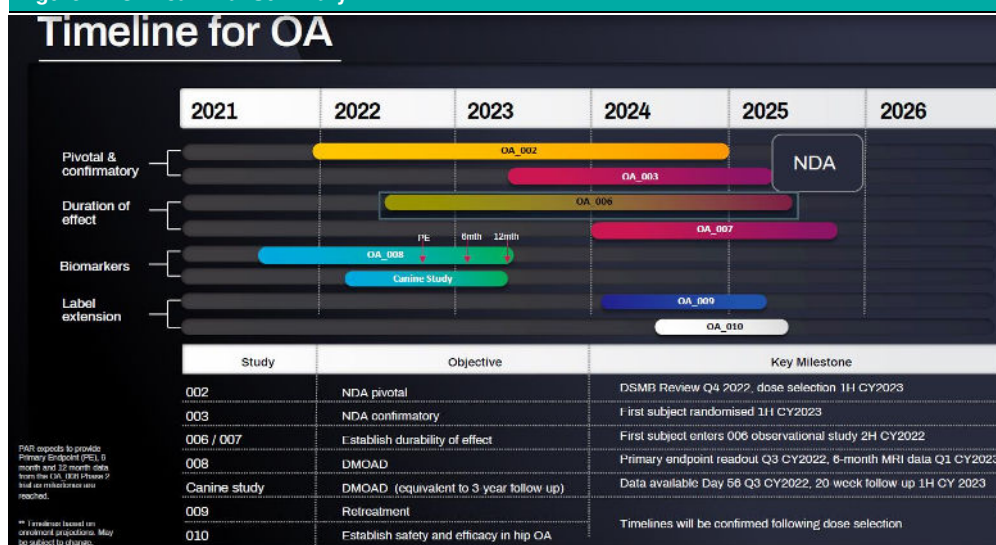
The headline data includes only brief detail in relation to the secondary endpoints associated with reductions in pain.

In respect of the cohort for twice weekly iPPS:

- mean percentage change from baseline WOMAC pain was 50% compared to 30% on placebo (p=0.05). The proportions achieving  $\geq 30\%$  and  $\geq 50\%$  improvements in pain were 73% and 60% respectively; and
- mean percentage change from baseline WOMAC function is 50% compared to 25% for placebo (p=0.017).

The reduction in pain reported here is consistent with previous studies, notably the earlier phase 2 in 112 patients in which 46% of subjects receiving iPPS showed a greater than 50% reduction in pain from baseline KOOS<sup>3</sup>.

**Figure 1 - Clinical Trial Summary**



SOURCE: COMPANY DATA

<sup>3</sup> The earlier trial measure pain score using the alternative KOOS rating score – Knee injury and osteoarthritis outcome score. Investigators subsequently changed to the WOMAC rating system which is more universally accepted in the United States and Europe.

# Paradigm Biopharmaceuticals

Paradigm Biopharmaceuticals is an Australia biotechnology company focused on repurposing Pentosan Polysulfate Sodium (PPS) for the treatment of Osteoarthritis (OA) in the knee. If approved the drug will have the brand name Zilosul.

The global market for a safe, effective treatment that provides superior patient outcomes compared to the standard of care is a multiple blockbuster. The recently completed phase II study produced some highly encouraging results that are worthy of further clinical trials.

In the US along the incidence of moderate to severe osteoarthritis is estimated at 30m persons. The pricing of the drug will ultimately be determined by the economic benefit associated with its use as well as the cost of other therapies. The conservative estimate is US\$2,500 per year which places the addressable market in the tens of billions of US\$.

## PROGRESS IN THE CLINIC

December 2018 - PAR announced headline results from its phase 2b randomised, double blind, placebo controlled multicentre trial, investigating subjects with Osteoarthritis and concurrent Bone Marrow Edema (BME) lesions (n=112). The trial met the clinical endpoint of change in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain achieving both clinically meaningful and statistically significant results between placebo and PPS.

The headline results were followed up with strong signals of efficacy in the secondary endpoints (including KOOS function). This phase II trial was conducted at 6 sites in Australia.

## PATHWAY TO APPROVAL

The company is pursuing a 505(b)2 registration pathway in the US. PAR is now enrolling patients in the first arm of a clinical trial.

## ADJACENT INDICATIONS

Paradigm recently executed an Exclusive In-License Agreement for the use of iPPS in the treatment of mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders. A key unmet medical need in this class of inherited disease is the lack of treatment of joint pain and dysfunction akin to osteoarthritis, hence the applicability of iPPS in treating these rare joint diseases. MPS is classified as an Orphan Indication/Designation in the US/EU and provides Paradigm the opportunity to serve a US\$1.4bn p.a. market that is in desperate need of new cost-effective treatments.

## KEY RISK AREAS

**Regulatory Pathway - PAR** is seeking registration for iPPS under the 505(b)2 regulatory pathway. The pathway is designed specifically for repurposed drugs including changes in dose form, strength, route of administration, formulation, dosing regimen or indication. This proposed repurposing of PPS has some rare characteristics.

- While the drug has been approved for years as an oral format and there is ample safety data, the proposed format, the dose and the indication (being OA) are all new.
- There is also the issue of the opioid crisis. PPS is a non steroid, non opioid, non addictive substance that has been shown to have a significant impact of pain levels associated with OA. It may help to reduce the accidental deaths from opioid overdose.
- PAR intends to conduct two phase 3 studies, one pivotal study of 900 subjects and a confirmatory phase 3 study of ~700 subjects.
- PAR will present a comprehensive set of safety data from the recent Phase II trial together with data from subjects treated in the compassionate use program and two phase 3 trials, thus representing a safety set of nearly 1,700 subjects. The evidence of

treatment will be established from two adequate and well controlled studies and further supported by the phases 2 data set.

**Intellectual Property**

- The company has several patents over the formulation and dosing on iPPS for the treatment of OA. The validity of these patents is highly likely to be challenged at some point, especially if the drug is a commercial success.
- The company has an exclusive supply contract with Bene Pharmaceuticals (Bene). We understand the exclusivity applies to human use only (excludes veterinary use). Bene holds the only drug Masterfile with the FDA to manufacture PPS. This supply contract represents a crucial piece of the company's value as it effectively prevents or delays the creation of generics.
- We are not aware of the contractual conditions that may lead to a termination of this contract (if any).
- We understand there are some other manufacturers of PPS, however, these products are not registered for human use and may not be referenced in any application for registration for human use. We understand the primary use of these products is veterinary.

**Clinical Risk**

- The efficacy of iPPS has not been validated in a large, multicentre, randomised, controlled clinical trial. There is no guarantee that the results from earlier studies will be repeated in a larger phase III study.

**Commercial Validation**

- Our valuation makes assumptions regarding selling price and volume in relation to future revenues from the sale of iPPS. In order for physicians to prescribe the drug and for payers to offer reimbursement, the clinical trials will need to demonstrate clinically significant improvement over the standard of care i.e. meaningful improvement in patient quality of life for pain reduction, side effect management and mobility amongst others. Early indicators based on the data from the phase II study are encouraging.

# Paradigm Biopharmaceuticals

as at 9 December 2021

Recommendation Buy, Speculative  
Price \$1.31  
Valuation \$2.20

Table 2 - Financial summary

Profit & Loss (A\$m)	FY21	FY22	FY23e	FY24e	FY25e
<b>Year Ending June</b>					
Risk adjusted revenues	-	-	-	64.5	62.2
COGS (Bene Royalty expense)	-	-	-	(2.2)	(2.1)
Gross profit	0.0	-0.1	0.0	63.2	61.0
GP margin	na	0%	na	0%	98%
R&D incentive	8.9	8.7	12.0	10.0	-
Other expenses	-43.2	-48.0	-71.0	-61.0	-21.0
EBITDA	-34.3	-39.4	-59.0	12.2	40.0
Depreciation	-	-	-	-	-
Amortisation	-	-	-	-	-
<b>EBIT</b>	<b>-34.3</b>	<b>-39.4</b>	<b>-59.0</b>	<b>12.2</b>	<b>40.0</b>
Finance income	-	-	0.5	0.5	0.5
<b>Pre tax profit</b>	<b>-34.3</b>	<b>-39.4</b>	<b>-58.5</b>	<b>12.7</b>	<b>40.5</b>
Tax expense	-	-	-	-	-
<b>NPAT - reported</b>	<b>-34.3</b>	<b>-39.4</b>	<b>-58.5</b>	<b>12.7</b>	<b>40.5</b>
<b>Cashflow (A\$m)</b>	<b>FY21</b>	<b>FY22</b>	<b>FY23e</b>	<b>FY24e</b>	<b>FY25e</b>
Gross cashflow	-35.1	-32.2	-62.4	12.2	40.0
Net interest	0.2	0.0	0.5	0.5	0.5
Tax paid	0.0	0.0	0.0	0.0	0.0
<b>Operating cash flow</b>	<b>-34.9</b>	<b>-32.2</b>	<b>-61.9</b>	<b>12.7</b>	<b>40.5</b>
Maintenance capex	0.0	0.0	0.0	0.0	0.0
Capitalised clinical trial spend	0.0	0.0	0.0	0.0	0.0
<b>Free cash flow</b>	<b>-34.9</b>	<b>-32.2</b>	<b>-61.9</b>	<b>12.7</b>	<b>40.5</b>
Business acquisitions	0.0	0.0	0.0	0.0	0.0
Proceeds from issuance	1.0	0.1	63.4	0.0	0.0
Movement in debt	0.0	0.1	-0.2	-0.2	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0
<b>Change in cash held</b>	<b>(33.9)</b>	<b>(32.0)</b>	<b>1.3</b>	<b>12.5</b>	<b>40.5</b>
Cash at beginning of period	104.0	71.0	39.7	41.0	53.5
<b>Cash at year end</b>	<b>71.0</b>	<b>39.7</b>	<b>41.0</b>	<b>53.5</b>	<b>94.0</b>
<b>Balance Sheet (A\$m)</b>	<b>FY21</b>	<b>FY22</b>	<b>FY23e</b>	<b>FY24e</b>	<b>FY25e</b>
Cash	71.0	39.7	41.0	53.5	94.0
Receivables	8.5	6.7	8.0	8.0	8.0
Other current assets	1.4	0.8	0.8	0.8	0.8
Intangibles	3.0	3.0	3.0	3.0	3.0
Other	1.0	0.5	0.5	0.5	0.5
<b>Total assets</b>	<b>84.8</b>	<b>50.7</b>	<b>53.3</b>	<b>65.8</b>	<b>106.3</b>
Trade payables	5.0	7.1	5.0	5.0	5.0
Debt (leases)	0.8	0.6	0.4	0.2	0.2
Other provisions	0.7	0.7	0.7	0.7	0.7
<b>Total Liabilities</b>	<b>6.5</b>	<b>8.4</b>	<b>6.1</b>	<b>5.9</b>	<b>5.9</b>
<b>Net Assets</b>	<b>78.3</b>	<b>42.3</b>	<b>47.2</b>	<b>60.0</b>	<b>100.4</b>
Share capital	147.0	147.1	210.5	210.5	210.5
Retained earnings	(75.2)	(114.1)	(172.6)	(159.9)	(119.4)
Reserves	6.5	9.3	9.3	9.3	9.3
<b>Shareholders Equity</b>	<b>78.3</b>	<b>42.3</b>	<b>47.2</b>	<b>60.0</b>	<b>100.4</b>

Last sale 09/12/2022	1.31				
Recommendation	Buy (Spec)				
Issued Capital	280.0				
Market Cap	366.8				
<b>Valuation Ratios (A\$m)</b>	<b>FY21</b>	<b>FY22</b>	<b>FY23e</b>	<b>FY24e</b>	<b>FY25e</b>
Reported EPS (cps)	-14.9	-16.9	-20.0	4.4	13.9
Normalised EPS (cps)	-14.9	-16.9	-20.0	4.4	13.9
EPS growth (%)	na	na	na	na	218%
<b>PE(x)</b>	<b>nm</b>	<b>nm</b>	<b>nm</b>	<b>30.1</b>	<b>9.5</b>
<b>EV/EBITDA (x)</b>	<b>nm</b>	<b>nm</b>	<b>nm</b>	<b>22.5</b>	<b>6.9</b>
<b>EV/EBIT (x)</b>	<b>nm</b>	<b>nm</b>	<b>nm</b>	<b>22.5</b>	<b>6.9</b>
NTA (cps)	32.8	16.9	15.6	20.1	34.4
P/NTA (x)	0.0	0.1	0.1	0.1	0.0
Book Value (cps)	34.1	18.2	16.7	21.1	35.4
Price/Book (x)	0.0	0.1	0.1	0.1	0.0
DPS (cps)	-	-	-	-	-
Payout ratio %	0%	0%	0%	0%	0%
Dividend Yield %	0.0%	0.0%	0.0%	0.0%	0.0%
Franking %	0%	0%	0%	0%	0%
FCF yield %	nm	nm	nm	343%	1089%
Net debt/Equity	0%	0%	0%	0%	0%
Net debt/Assets	0%	0%	0%	0%	0%
Gearing	net cash	net cash	net cash	net cash	net cash
Net debt/EBITDA (x)	n/a	n/a	n/a	n/a	n/a
Interest cover (x)	n/a	n/a	n/a	n/a	n/a

Interim Results (A\$m)	1H22	2H22	1H23e	2H23e
Revenues from product sales	-	-	-	-
R&D Rebate	-	8.7	-	12.0
Operating expenses	(27.0)	(21.0)	(30.5)	(40.5)
EBIT	(27.0)	(12.3)	-	-

SOURCE: BELL POTTER SECURITIES ESTIMATES



**Recommendation structure**

**Buy:** Expect >15% total return on a 12 month view. For stocks regarded as 'Speculative' a return of >30% is expected.

**Hold:** Expect total return between -5% and 15% on a 12 month view

**Sell:** Expect <-5% total return on a 12 month view

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*Such investments may carry an exceptionally high level of capital risk and volatility of returns.*

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Disclosure: Bell Potter Securities acted as lead manager of the company's August 2022 capital raise for \$66m and received fees for that service.

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The fact that the intellectual property base of a typical biotechnology company lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology investments ought to be regarded. Clinical and regulatory risks are inherent in biotechnology stocks. Biotechnology developers usually seek U.S. FDA approval for their technology which is a long and arduous three phase process to prove the safety, effectiveness and appropriate application or use of the developed drug and even after approval a drug can be the subject of an FDA investigation of subsequently discovered possible links between the drug and other diseases not previously diagnosed. Furthermore, the Australian exchange listed biotechnology sector is subject to influence by the global biotechnology sector, particularly that in the USA. Consequently, Australian exchange listed biotechnology stocks can experience sharp movements, both upwards and downwards, in both valuations and share prices, as a result of a re-rating of the sector both globally and in the USA, in particular. Investors are advised to be cognisant of these risks before buying such a stock.

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