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**CIRCADIAN  
TECHNOLOGIES  
LIMITED**

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**FACSIMILE HEADER**

**DATE:** 30 JANUARY 2001  
**FROM:** CIRCADIAN TECHNOLOGIES LIMITED  
**TO:** THE MANAGER COMPANIES SECTION  
AUSTRALIAN STOCK EXCHANGE LIMITED  
**FAX NO:** 1300 300 021  
**NO. OF PAGES:** 35 (including this sheet)

Dear Sir/Madam

**Re: 31 December 2000 Half Yearly Report**

In accordance with Listing Rule 4.1 we enclose the Half Yearly Report (Appendix 4B) (reviewed) of the consolidated results of Circadian Technologies Limited for the six months to 31 December 2000, review of operations (extracted from the directors' report), directors' report, directors' declaration and our auditor's independent review report.

The Directors report a net consolidated loss after income tax for the period of \$592,600 (1999: consolidated loss after tax: \$810,635). The loss is after fully expensing research and development and patenting expenditure during the period under review.

The company has no borrowings.

Yours faithfully  
CIRCADIAN TECHNOLOGIES LIMITED

NATALIE KORCHEV  
COMPANY SECRETARY

**CIRCADIAN TECHNOLOGIES LIMITED**  
**REVIEW OF OPERATIONS – HALF YEAR ENDED 31 DECEMBER 2000**  
**(Extracted from the Directors' Report)**

In July 2000, Circadian completed a share placement of 5,300,000 ordinary shares at an issue price of \$4.50 per share for the purpose of providing working capital to fund development of technology and investment in technology related projects and opportunities. This increased the company's share capital by \$22,913,663 (net of directly related costs on the issue of equity) to \$49,718,710.

The economic entity experienced a decrease in operating loss before abnormal items in the current period compared to the previous half year period predominantly due to an increase in interest income, which was partly offset, by an increase in research and development.

Detailed below is an update on the consolidated entity's interests in listed technology holdings and research and development projects for the half year ended 31 December 2000. The 30 June 2000 annual report contains detailed background information relating to these holdings and projects.

**Metabolic Pharmaceuticals Limited – Advanced Obesity Drug and Type II Diabetes Projects**

***Circadian Holding - Market Value 31 December 2000: \$28.08 million; Book value: \$Nil***

***Shareholders: Circadian: 38.5%; Monash: 25.6%; Others: 35.9%***

Metabolic Pharmaceuticals Limited ("Metabolic") has advised the following through their public announcements:

- AOD9604 Obesity Drug: Pre-clinical toxicology tests of compound AOD9604 were successfully completed and the Ethics Review Board at Medeval, Metabolic's UK Clinical Trials Contractor, "has given its approval for the conduct of Metabolic's planned Phase I human clinical trial of the obesity drug".

Dosing of the first volunteer is expected to begin around 7 February 2001 and the trial, to be conducted with a total of 16 volunteers, is expected to be completed about 12 April with results available shortly thereafter.

- Veterinary Applications of AOD9604: As previously advised, Metabolic is assessing the potential veterinary applications of the AOD technology, and is initially investigating its application to reduction of back fat in pigs.

Metabolic now has small quantities of a prototype food additive produced under contract at CSIRO, which on preliminary investigation appear to contain useful quantities of AOD. Further laboratory analysis is under way.

- In December SemBioSys executed a funded feasibility study agreement with Metabolic. Under the terms of the agreement, SemBioSys will evaluate the feasibility of producing Metabolic's proprietary anti-obesity peptide AOD9604 using SemBioSys' patented oil body/oleosin protein production platform.

If the clinical trials of Metabolic's obesity drug AOD9604 are successful, multi-tonne quantities of pharmaceutical grade AOD9604 will need to be produced at low cost. Metabolic believes that the SemBioSys process has the greatest potential to meet these requirements.

SemBioSys is a Calgary-based biotechnology company focused on the development of high value protein and oil body based products using its proprietary oil body/oleosin technology. The company was spun out of the University of Calgary in 1996.

Metabolic's half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

**Axon Instruments Inc (USA)** - **Developers and manufacturers of genomics and bio-informatics products**  
- **World Market Leader in Instrumentation and Software for Cellular Electrophysiology**

*Circadian Holding – Market Value 31 December 2000: \$101.5 million; Book Value: \$1.4 million*  
*Shareholders: Circadian: 15.8%; Others: 84.2%*

Highlights from Axon Instruments Inc ("Axon") shareholder update released on 2 November 2000:

- In July, Axon signed an agreement with the CSIRO for the development of advanced bioinformatics and imaging algorithms which will be relevant for its products Javelin (bioinformatics software that manages and analyses the large amounts of data produced by microarray scanners such as GenePix) and CellPix (optically scans a multi-well plate to measure the effects of many different drug candidates on biological materials in the wells).
- In August, Axon completed a placement of 39,062,500 ordinary shares at an issue price of \$1.28 per share to raise a total of \$50 million. The purpose of the placement was to fund the commercialisation and acquisition of intellectual property for next generation cell-based screening, and proteomics; research and development of consumables for proteomics and cell-based screening products.
- Axon recently signed an exclusive worldwide license agreement and research collaboration with Yale University (US) for a revolutionary high-throughput patch clamp technology. Axon will fund ongoing research into the technology at Yale University, and has secured the rights to downstream technology developed from the research. Axon plans to use this technology as the core component in a device (known as RoboPatch) for screening pharmaceutical agents acting on mammalian cell-membranes ion-channels and transporters. Ion channel activity is important for studying many medical disorders, including migraine, epilepsy, irregular heartbeat and cystic fibrosis.

Currently, pharmaceutical screening of important ion-channel drugs is inefficient because the techniques are indirect. Axon's device has the potential to resolve a major bottleneck in the drug discovery process.

- In August, Roche Biosciences, part of Roche Pharmaceuticals Research, joined Axon's consortium for the development of RoboClamp (a high throughput electrophysiology screening system to be mostly used in the drug discovery market). Roche has extensive experience in high throughput screening, and Axon expects them to provide valuable product evaluation.
- In October, the Parke-Davis division of Pfizer joined Axon's consortium for the development of CellPix. Parke-Davis joins existing members AstraZeneca, Geron Corp and Cytokinetics.

Axon's annual report for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

### **Optiscan Imaging Limited - Early Cancer Detection**

***Circadian Holding - Market Value 31 December 2000: \$11.02 million; Book value: \$361,132***

***Shareholders: Circadian: 10.1%; Axon: 15.4%; Others: 74.5%***

Optiscan Imaging Limited ("Optiscan") has advised the following in their annual report released in October 2000 and in their public announcement dated 16 January 2001:

- **Hand Held Probe** (Annual Report)  
The release of the hand held probe is impending. Optiscan anticipates that uptake by the conservative medical marketplace will remain modest in the short to medium term. During this time, Optiscan will engage in significant market development activity, focusing on the support of early adopters and medical opinion leaders in their use of the probes. This will be aimed at ensuring that the growing realm of uses is realised in clinical practice, increasing the appeal of the product to the broader dermatological community. Achievement of substantial market penetration as a result of this process is likely to result over a two to three year period. As such, Optiscan will continue to be associated with multiple trials well beyond the actual release of the product.
- **Flexible Probe** (Annual Report)  
Progress has continued to be made in miniaturisation of scanning mechanisms for the flexible probe. This project is on track to construct advanced prototype probes for clinical trial in the 2001 calendar year.

Potential applications in gastroenterology include: colon cancer, mouth cancer, gastric cancer, Barrett's oesophagus, ulcerative colitis and cancer management.

In parallel with the probe development, animal studies have been conducted to investigate several of these applications. With the use of several human-safe contrast agents, results of these investigations have been very encouraging.

- **Alliances** (Annual Report)  
Discussions with potential strategic allies and partners are continuing. The possibility exists for multiple partnering relationships including those associated with technology relating to consumables and telemedicine.

- **US FDA Update** (16 January 2001 ASX Announcement)

Optiscan has lodged its submission to the US Food & Drug Administration to distribute its optical-fibre microscopes in the USA. Mr Delaney confirmed that it was not unusual for the FDA to take several months before giving an answer.

According to Optiscan's Managing Director, Optiscan's product faces low regulatory barriers because it is not hazardous to patients, it is not implanted and therefore does not come into contact with internal tissue, and the instrument does not make diagnostic decisions on behalf of clinicians. Traditionally, the FDA looks favourably on such products.

Optiscan technology has been used for research purposes in the US for several months including at the prestigious Centre for Biologic Imaging at the University of Pittsburgh. Optiscan's Managing Director said: "Optiscan plans to widen its clinical trials this year to include its second product, which is for gastroenterology. The company is presently making pleasing and positive headway with its skin cancer trials."

Optiscan's half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

#### **Syngene Limited - Gene Diagnostics**

*Shareholders: Circadian: 42.4%; Casthree Pty Ltd: 20%; Howard Florey Institute: 19.5%; Howard Florey Institute staff and others: 18.1%*

- Negotiations are continuing with a major US medical diagnostic company, which may require a non-exclusive worldwide license in respect of one of Syngene's patents in the area of in situ hybridization. In situ hybridisation locates precise gene activity in sections of tissue and caters to diagnostic markets. The market for DNA therapeutics and diagnostics is expected to show substantial growth especially in light of the recent completion of the first draft map of the Human Genome. The patent was granted in the US in 1997, providing Syngene with 17 years protection to 2014 in the US. Patents have also been granted in Europe, Canada, Japan and Australia.
- Polychip's interest was diluted to 42.4% as a result of an issue of shares to Casthree Pty Ltd (a subsidiary of Consolidated Press Holdings Limited).

#### **Antisense Therapeutics Limited - Gene Directed Therapeutics**

- Antisense Therapeutics Limited ('ATL') was incorporated on 13 November 2000 to develop antisense technologies.
- Antisense cell therapy relates to the field of gene therapy whereby synthetic genetic material may be used to block the action of genes that produce disease-causing proteins. A possible advantage of antisense drugs over conventional drugs is that antisense has the potential to be rationally designed with acknowledge of the genetic target, whereas conventional drugs are found typically by a process of extensive trial and error. Interest in antisense technologies has been fuelled by the rapid growth and understanding of the science of genomics (including the Human Genome Project, which provides a source of gene sequence data for rational drug design using antisense).

ATL is presently formulating several innovative projects, which relate to the use of antisense technology and potential collaborations in this area are in the process of negotiation.

Further capital will be required in the forthcoming period for these antisense activities and consequently a listing may be sought on the Australian Stock Exchange, the precise timing of which will depend on the progress of the projects and collaborations relating to these expanded activities.

### **AMRAD Corporation Limited**

***Circadian Holding - Market Value 31 December 2000: \$17.5 million; Book value: \$16.6 million***

***Shareholders: Circadian: 17.6%; Others: 82.4%***

- Circadian's wholly owned controlled entity Fibre Optics (Aust) Pty Ltd increased its holding in AMRAD Corporation Limited ("AMRAD") from 10% at 30 June 2000 to 17.6% at period end. Since 31 December 2000 the holding has increased to 19.12%.
- AMRAD is a listed biotechnology research and development company and is one of Australia's oldest biotechnology companies established by the Victorian Government and four Melbourne based medical institutions in 1986, eventually listing in 1996. AMRAD was founded to commercialise medical discoveries from Victorian research institutions.

AMRAD's half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

### **Meloma Pty Ltd - Cancer Diagnostic/Therapeutics**

***Shareholders: Circadian: 30%; Inventors and Others: 70%***

- On 8 December 2000 Fibre Optics (Aust) Pty Ltd, a wholly owned subsidiary of Circadian, together with the inventing scientists incorporated Meloma Pty Ltd with Fibre Optics providing \$400,000 for research funding.

Meloma has the rights (patent application) to a novel method for rapid identification and detection of cancer-specific antigens. The methodology may have applications for a broad range of cancers, including breast, ovarian, colorectal and prostate cancers. A provisional patent application covering the technology has been lodged.

Researchers are being appointed for the development of new blood tests for cancer detection, which may also have potential for new therapeutic products. It is expected that the first phase of the research programme will be completed later this calendar year.

The market for cancer tests is substantial and current tests in most cases are unsatisfactory.

### **Cancer Research Projects - XR5000**

*Circadian interest: 16.67% of any scheduled milestone payments and royalties of 2% of sales made by Xenova*

Highlights from Xenova Plc's ("Xenova") public announcements for the period:

#### **XR5000 Phase II Human Clinical Trials**

- Xenova raised £10 million in a public offer during the period. Part of the proceeds will be applied towards the completion of Phase II clinical trials and, if appropriate, together with a partner, conducting Phase III trials for XR5000.
- Phase II human clinical trials for ovarian, non-small lung and glioma cancers are in progress. Final data from these three remaining studies are expected to be available shortly. Results from these trials will help determine the future development strategy for this compound.

#### **XR5000 Second Generation Drug Leads**

- A patent application has been made relating to XR5000 second generation drug leads. This includes XR5944, which is part of this family of drug leads.

### **Gene Directed Enzyme Prodrug Therapy Technology Project 'GDEPT' – Cancer Research Project**

*Circadian: entitled to 30% of net income due to Auckland Division Cancer Society of New Zealand Inc ('Society')*

#### ***Background:***

An agreement was signed on 10 April 1996 between Circadian and the Society in relation to the GDEPT project, whereby Circadian is entitled to 30% of all royalties and milestones and any other entitlements due to the Society.

Most anticancer drugs are cytotoxic agents, which distribute widely in the body and selectively kill dividing cells (rather than only cancer cells). Such drugs are limited in their efficacy by the necessity to restrict the damage they cause to rapidly dividing normal cells. To achieve further substantial improvements in efficacy, more selective approaches are required. One is to use non-toxic prodrug forms of cytotoxic agents, and activate these selectively in tumours. This can be achieved in principle by incorporating a non-human gene into the tumour cells, so that these cells selectively produce a non-human enzyme that is able to activate the prodrug (a drug that requires further metabolism before becoming biologically active). Prodrugs suitable for this approach must be non-toxic, and able to be activated selectively only by the chosen non-human enzyme to release a very potent cytotoxin. Vion Pharmaceuticals Inc, Onyx Pharmaceuticals Inc and AstraZeneca are involved in the project. Circadian has no further funding commitments relating to this project.

#### **Analgesic Project - Non-Sedating Analgesics**

*Project Owners: Circadian: 85.7%; Monash University: 14.3%*

- Ongoing development and testing has continued during the period at Monash University.

- Circadian extended the funding for the project by an additional 3 months to March 2001. The additional funding amounts to \$21,890.

#### **Yeast Mediated Reactions Project (Ephedrine)**

*Project Owners: Circadian: 60%; Victoria University of Technology: 40%*

- Work is continuing on the new method of producing ephedrine. Circadian is now funding the second phase of the project for a further 12 month period to 1 October 2001, in accordance with the original research and development agreement. The funding amounts to \$51,000 for research and development plus \$54,000 for equipment.
- Circadian's interest in the project increased from 50% to 60% during the period under review.

#### **Circadian Rhythm Disorders Project**

*Project Owners: Circadian: 60%; Monash: 40%*

- Eli Lilly and Company ("Lilly") have a non-exclusive worldwide license in respect of the patents and negotiations are being conducted at present with several parties regarding licensing the further development of Lilly's melatonin analogue to complete more definitive phase II human studies. The analogue has been studied by Lilly in two early Phase II studies.

# Appendix 4B (rule 4.13(b))

## Half yearly/preliminary final report

Introduced 1/7/2000.

Name of entity

CIRCADIAN TECHNOLOGIES LIMITED

ACN, ARBN or ARSN	Half yearly (tick)	Preliminary final (tick)	Half year/financial year ended ('current period')
006 340 567	X		31 December 2000

### For announcement to the market

Extracts from this report for announcement to the market (see note 1).

\$A

Revenues from ordinary activities (item 1.1)	Up	554%	to	903
Profit (loss) from ordinary activities after tax (before amortisation of goodwill) attributable to members (item 1.20)	Down	27%	to	(593)
Profit (loss) from ordinary activities after tax attributable to members (item 1.23)	Down	27%	to	(593)
Profit (loss) from extraordinary items after tax attributable to members (item 2.5(d))	Gain (loss) of	-		-
Net profit (loss) for the period attributable to members (item 1.11)	Down	27%	to	(593)

Dividends (distributions)	Amount per security	Franked amount per security
Final dividend (Preliminary final report only - item 15.4) Interim dividend (Half yearly report only - item 15.6)	- ¢	- ¢
Previous corresponding period (Preliminary final report - item 15.5; half yearly report - item 15.7)	- ¢	- ¢

+Record date for determining entitlements to the dividend, (in the case of a trust, distribution) (see item 15.2)

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Brief explanation of omission of directional and percentage changes to profit in accordance with Note 1 and short details of any bonus or cash issue or other item(s) of importance not previously released to the market:

+ See chapter 19 for defined terms.

### Consolidated profit and loss account

	Current period - \$A'000	Previous corresponding period - \$A'000
1.1 Revenues from ordinary activities	903	138
1.2 Expenses from ordinary activities (see items 1.24 + 12.5 + 12.6)	(1,500)	(949)
1.3 Borrowing costs	(11)	-
1.4 Share of net profit (loss) of associates and joint venture entities (see item 16.7)	15	-
<b>1.5 Profit (loss) from ordinary activities before tax</b>	<b>(593)</b>	<b>(811)</b>
1.6 Income tax on ordinary activities (see note 4)	-	-
<b>1.7 Profit (loss) from ordinary activities after tax</b>	<b>(593)</b>	<b>(811)</b>
1.8 Profit (loss) from extraordinary items after tax (see item 2.5)	-	-
<b>1.9 Net profit (loss)</b>	<b>(593)</b>	<b>(811)</b>
1.10 Net profit (loss) attributable to outside +equity interests	-	-
<b>1.11 Net profit (loss) for the period attributable to members</b>	<b>(593)</b>	<b>(811)</b>

### Consolidated retained profits

1.12 Retained profits (accumulated losses) at the beginning of the financial period	(3,074)	(4,297)
1.13 Net profit (loss) attributable to members (item 1.11)	(593)	(811)
1.14 Net transfers to and from reserves	-	-
1.15 Net effect of changes in accounting policies	-	-
1.16 Dividends and other equity distributions paid or payable	-	-
<b>1.17 Retained profits (accumulated losses) at end of financial period</b>	<b>(3,667)</b>	<b>(5,108)</b>

### Profit restated to exclude Amortisation of goodwill

	Current period \$A'000	Previous corresponding period \$A'000
1.18 Profit (loss) from ordinary activities after tax before outside equity interests (items 1.7) and amortisation of goodwill	(593)	(805)
1.19 Less (plus) outside +equity interests	-	-
<b>1.20 Profit (loss) from ordinary activities after tax (before amortisation of goodwill) attributable to members</b>	<b>(593)</b>	<b>(805)</b>

+ See chapter 19 for defined terms.

**Profit (loss) from ordinary activities attributable to members**

	Current period \$A'000	Previous corresponding period \$A'000
1.21 Profit (loss) from ordinary activities after tax ( <i>item 1.7</i> )	(593)	(811)
1.22 Less (plus) outside +equity interests	-	-
<b>1.23 Profit (loss) from ordinary activities after tax, attributable to members</b>	<b>(593)</b>	<b>(811)</b>

**Revenue and expenses from ordinary activities**

*AASB 1004 requires disclosure of specific categories of revenue and AASB 1018 requires disclosure of expenses from ordinary activities according to either their nature of function. Entities must report details of revenue and expenses from ordinary activities using the layout employed in their accounts. See also items 12.1 to 12.6.*

	Current period \$A'000	Previous corresponding period \$A'000
1.24 Details of revenue and expenses		
Interest Income	893	112
Grant Income	-	14
Other revenue	10	13
Administrative Expenses	(1,023)	(791)
Occupancy Expenses	(41)	(29)
Patent expenses	(58)	(23)
Research and Development Expense	(378)	(106)
Depreciation Expense	(11)	(11)

+ See chapter 19 for defined terms.

## Intangible and extraordinary items

		<i>Consolidated - current period</i>			
		Before tax \$A'000  (a)	Related tax \$A'000  (b)	Related outside +equity interests \$A'000  (c)	Amount (after tax) attributable to members \$A'000  (d)
2.1	Amortisation of goodwill	-	-	-	-
2.2	Amortisation of other intangibles	-	-	-	-
<b>2.3</b>	<b>Total amortisation of intangibles</b>	-	-	-	-
2.4	Extraordinary items (details)	-	-	-	-
<b>2.5</b>	<b>Total extraordinary items</b>	-	-	-	-

### Comparison of half year profits

*(Preliminary final report only)*

		Current year - \$A'000	Previous year - \$A'000
3.1	Consolidated profit (loss) from ordinary activities after tax attributable to members reported for the 1st half year (item 1.23 in the half yearly report)	N/A	N/A
3.2	Consolidated profit (loss) from ordinary activities after tax attributable to members for the 2nd half year	N/A	N/A

+ See chapter 19 for defined terms.

<b>Consolidated balance sheet</b>		At end of current period \$A'000	As shown in last annual report \$A'000	As in last half yearly report \$A'000
<b>Current assets</b>				
4.1	Cash	25,981	14,260	4,452
4.2	Receivables	648	113	20
4.3	Investments	-	-	-
4.4	Inventories	-	-	-
4.5	Other (provide details if material)	19	25	10
<b>4.6</b>	<b>Total current assets</b>	<b>26,648</b>	<b>14,398</b>	<b>4,482</b>
<b>Non-current assets</b>				
4.7	Receivables	545	625	82
4.8	Investments (equity accounted)	671	657	-
4.9	Other investments	20,182	9,722	1,979
4.10	Inventories	-	-	-
4.11	Exploration and evaluation expenditure capitalised (see para .71 of AASB 1022)	-	-	-
4.12	Development properties (+mining entities)	-	-	-
4.13	Other property, plant and equipment (net)	86	85	88
4.14	Intangibles (net)	-	-	10
4.15	Other (provide details if material)	-	-	-
<b>4.16</b>	<b>Total non-current assets</b>	<b>21,484</b>	<b>11,089</b>	<b>2,159</b>
<b>4.17</b>	<b>Total assets</b>	<b>48,132</b>	<b>25,487</b>	<b>6,641</b>
<b>Current liabilities</b>				
4.18	Payables	234	244	29
4.19	Interest bearing liabilities	-	-	-
4.20	Provisions	68	48	44
4.21	Other (provide details if material)	-	-	-
<b>4.22</b>	<b>Total current liabilities</b>	<b>302</b>	<b>292</b>	<b>73</b>
<b>Non-current liabilities</b>				
4.23	Payables	-	-	-
4.24	Interest bearing liabilities	-	-	-
4.25	Provisions	127	73	73
4.26	Other (provide details if material)	-	-	-
<b>4.27</b>	<b>Total non-current liabilities</b>	<b>127</b>	<b>73</b>	<b>73</b>
<b>4.28</b>	<b>Total liabilities</b>	<b>429</b>	<b>365</b>	<b>146</b>
<b>4.29</b>	<b>Net assets</b>	<b>47,701</b>	<b>25,122</b>	<b>6,495</b>

+ See chapter 19 for defined terms.

**Appendix 4B (rule 4.13(b))**  
**Half yearly/preliminary final report**

**Consolidated balance sheet continued**

<b>Equity</b>				
4.30	Capital/contributed equity	49,977	26,805	10,869
4.31	Reserves	1,391	1,391	734
4.32	Retained profits (accumulated losses)	(3,667)	(3,074)	(5,108)
<b>4.33</b>	<b>Equity attributable to members of the parent entity</b>	<b>47,701</b>	<b>25,122</b>	<b>6,495</b>
4.34	Outside +equity interests in controlled entities	-	-	-
<b>4.35</b>	<b>Total equity</b>	<b>47,701</b>	<b>25,122</b>	<b>6,495</b>
4.36	Preference capital included as part of 4.33	-	-	-

**Exploration and evaluation expenditure capitalised**

*To be completed only by entities with mining interests if amounts are material. Include all expenditure incurred regardless of whether written off directly against profit.*

	Current period \$A'000	Previous corresponding period - \$A'000
5.1	Opening balance	-
5.2	Expenditure incurred during current period	-
5.3	Expenditure written off during current period	-
5.4	Acquisitions, disposals, revaluation increments, etc.	-
5.5	Expenditure transferred to Development Properties	-
<b>5.6</b>	<b>Closing balance as shown in the consolidated balance sheet (item 4.11)</b>	<b>-</b>

**Development properties**

*(To be completed only by entities with mining interests if amounts are material)*

	Current period \$A'000	Previous corresponding Period - \$A'000
6.1	Opening balance	-
6.2	Expenditure incurred during current period	-
6.3	Expenditure transferred from exploration and evaluation	-
6.4	Expenditure written off during current period	-
6.5	Acquisitions, disposals, revaluation increments, etc.	-
6.6	Expenditure transferred to mine properties	-
<b>6.7</b>	<b>Closing balance as shown in the consolidated balance sheet (item 4.12)</b>	<b>-</b>

+ See chapter 19 for defined terms.

## Consolidated statement of cash flows

		Current period \$A'000	Previous corresponding period - \$A'000
<b>Cash flows related to operating activities</b>			
7.1	Receipts from customers	-	-
7.2	Payments to suppliers and employees	(1,264)	(877)
7.3	Dividends received from associates	-	-
7.4	Other dividends received	-	-
7.5	Interest and other items of similar nature received	323	114
7.6	Interest and other costs of finance paid	(11)	(1)
7.7	Income taxes paid	-	-
7.8	Other (provide details if material) - grant income	10	44
<b>7.9</b>	<b>Net operating cash flows</b>	<b>(942)</b>	<b>(730)</b>
<b>Cash flows related to investing activities</b>			
7.10	Payment for purchases of property, plant and equipment	(15)	(16)
7.11	Proceeds from sale of property, plant and equipment	2	-
7.12	Payment for purchases of equity investments	(10,626)	-
7.13	Proceeds from sale of equity investments	50	-
7.14	Loans to other entities	-	-
7.15	Loans repaid by other entities	80	20
7.16	Other (provide details if material)	-	-
<b>7.17</b>	<b>Net investing cash flows</b>	<b>(10,509)</b>	<b>4</b>
<b>Cash flows related to financing activities</b>			
7.18	Proceeds from issues of +securities (shares, options, etc.)	24,108	150
7.19	Proceeds from borrowings	-	-
7.20	Repayment of borrowings	-	-
7.21	Dividends paid	-	-
7.22	Other (provide details if material) – Share placement fees	(936)	-
<b>7.23</b>	<b>Net financing cash flows</b>	<b>23,172</b>	<b>150</b>
<b>7.24</b>	<b>Net increase (decrease) in cash held</b>	<b>11,721</b>	<b>(576)</b>
7.25	Cash at beginning of period (see <i>Reconciliation of cash</i> )	14,260	5,028
7.26	Exchange rate adjustments to item 7.25.	-	-
<b>7.27</b>	<b>Cash at end of period</b> (see <i>Reconciliation of cash</i> )	<b>25,981</b>	<b>4,452</b>

+ See chapter 19 for defined terms.

## Non-cash financing and investing activities

Details of financing and investing transactions which have had a material effect on consolidated assets and liabilities but did not involve cash flows are as follows. If an amount is quantified, show comparative amount.

NIL
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## Reconciliation of cash

Reconciliation of cash at the end of the period (as shown in the consolidated statement of cash flows) to the related items in the accounts is as follows.	Current period \$A'000	Previous Corresponding Period - \$A'000
8.1 Cash on hand and at bank	981	183
8.2 Deposits at call	25,000	4,269
8.3 Bank overdraft	-	-
8.4 Other (provide details)	-	-
<b>8.5 Total cash at end of period (item 7.27)</b>	<b>25,981</b>	<b>4,452</b>

## Ratios

	Current period	Previous corresponding Period
<b>Profit before tax / revenue</b>		
9.1 Consolidated profit (loss) from ordinary activities before tax (item 1.5) as a percentage of revenue (item 1.1)	-	-
<b>Profit after tax / +equity interests</b>		
9.2 Consolidated net profit (loss) from ordinary activities after tax attributable to members (item 1.9) as a percentage of equity (similarly attributable) at the end of the period (item 4.33)	(1.2%)	(12.5%)

## Earnings per security (EPS)

	Current period	Previous corresponding period
10.1 Calculation of the following in accordance with AASB 1027: <i>Earnings per Share</i>		
(a) Basic EPS	(1.46) cents	(2.58) cents
(b) Diluted EPS (if materially different from (a))	-	-
(c) Weighted average number of ordinary shares outstanding during the period used in the calculation of the Basic EPS	40,532	31,410

## NTA backing

(see note 7)	Current period	Previous corresponding period
11.1 Net tangible asset backing per +ordinary security	116.24 cents	20.59 cents

+ See chapter 19 for defined terms.

**Details of specific receipts/outlays, revenues/ expenses**

	Current period \$A'000	Previous corresponding period - \$A'000
12.1 Interest revenue included in determining item 1.5	893	112
12.2 Interest revenue included in item 12.1 but not yet received (if material)	633	9
12.3 Interest costs excluded from borrowing costs, capitalised in asset values	3	-
12.4 Outlays (except those arising from the +acquisition of an existing business) capitalised in intangibles (if material)	-	-
12.5 Depreciation and amortisation (excluding amortisation of intangibles)	-	-
12.6 Other specific relevant items not shown in item 1.24 (see note 15)	11	11

**Control gained over entities having material effect**

13.1 Name of entity (or group of entities)	-
13.2 Consolidated profit (loss) from ordinary activities and extraordinary items after tax of the entity (or group of entities) since the date in the current period on which control was +acquired	\$ -
13.3 Date from which such profit has been calculated	\$ -
13.4 Profit (loss) from ordinary activities and extraordinary items after tax of the entity (or group of entities) for the whole of the previous corresponding period	\$ -

+ See chapter 19 for defined terms.

**Loss of control of entities having material effect**

14.1	Name of entity (or group of entities)	N/A
14.2	Consolidated profit (loss) from ordinary activities and extraordinary items after tax of the entity (or group of entities) for the current period to the date of loss of control	N/A
14.3	Date to which the profit (loss) in item 14.2 has been calculated	N/A
14.4	Consolidated profit (loss) from ordinary activities and extraordinary items after tax of the entity (or group of entities) while controlled during the whole of the previous corresponding period	N/A
14.5	Contribution to consolidated profit (loss) from ordinary activities and extraordinary items from sale of interest leading to loss of control	N/A

**Reports for industry and geographical segments**

*Information on the industry and geographical segments of the entity must be reported for the current period in accordance with AASB 1005: Financial Reporting by Segments. Because of the different structures employed by entities, a pro forma is not provided. Segment information should be completed separately and attached to this report. However, the following is the presentation adopted in the Appendices to AASB 1005 and indicates which amounts should agree with items included elsewhere in this report.*

**Circadian Technologies Limited** operates in one industry and one geographical segment, those being the medical, technology and healthcare industry and Australia respectively.

**Segments**

Operating Revenue

Sales to customers outside the economic entity

Inter-segment sales

Unallocated revenue

Total revenue

Segment result

Unallocated expenses

Consolidated profit (loss) from ordinary activities before tax (equal to item 1.5)

Segment assets	)	<i>Comparative data for segment assets should be as at the end of the previous corresponding period.</i>
Unallocated assets	)	
Total assets (equal to item 4.17)	)	

**Dividends (in the case of a trust, distributions)**

15.1	Date the dividend (distribution) is payable	-
15.2	+Record date to determine entitlements to the dividend (distribution) (ie, on the basis of registrable transfers received by 5.00 pm if +securities are not +CHESS approved, or security holding balances established by 5.00 pm or such later time permitted by SCH Business Rules if +securities are +CHESS approved)	-
15.3	If it is a final dividend, has it been declared? (Preliminary final report only)	-

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+ See chapter 19 for defined terms.

**Amount per security**

		Amount per security	Franked amount per security at 36% tax	Amount per security of foreign source dividend
<b>15.4</b>	<i>(Preliminary final report only)</i> <b>Final dividend:</b> Current year	- ¢	- ¢	- ¢
	15.5 Previous year	- ¢	- ¢	- ¢
<b>15.6</b>	<i>(Half yearly and preliminary final reports)</i> <b>Interim dividend:</b> Current year	- ¢	- ¢	- ¢
	15.7 Previous year	- ¢	- ¢	- ¢

**Total dividend (distribution) per security (interim plus final)**

(Preliminary final report only)

	Current year	Previous year
15.8 +Ordinary securities	- ¢	- ¢
15.9 Preference +securities	- ¢	- ¢

**Half yearly report - interim dividend (distribution) on all securities or Preliminary final report - final dividend (distribution) on all securities**

	Current period \$A'000	Previous corresponding period - \$A'000
15.10 +Ordinary securities	-	-
15.11 Preference +securities	-	-
15.12 Other equity instruments	-	-
<b>15.13 Total</b>	-	-

The +dividend or distribution plans shown below are in operation.

NIL
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The last date(s) for receipt of election notices for the +dividend or distribution plans

-
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Any other disclosures in relation to dividends (distributions)

NIL
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+ See chapter 19 for defined terms.

## Details of aggregate share of profits (losses) of associates and joint venture entities

	Current period \$A'000	Previous corresponding period - \$A'000
16.1 Profit (loss) from ordinary activities before income tax	34	-
16.2 Income tax on ordinary activities	-	-
<b>16.3 Profit (loss) from ordinary activities after income tax</b>	<b>34</b>	<b>-</b>
16.4 Extraordinary items net of tax	-	-
<b>16.5 Net profit (loss)</b>	<b>34</b>	<b>-</b>
16.6 Outside +equity interests	(20)	-
<b>16.7 Net profit (loss) attributable to members</b>	<b>14</b>	<b>-</b>

## Material interests in entities which are not controlled entities

The economic entity has an interest (that is material to it) in the following entities. If the interest was acquired or disposed of during either the current or previous corresponding period, indicate date of acquisition ("from xx/xx/xx") or disposal ("to xx/xx/xx").

Name of entity	Percentage of ownership interest held at end of period or date of disposal		Contribution to net profit (loss) (item 1.9)	
	Current period	Previous corresponding period	Current period - \$A'000	Previous corresponding period - \$A'000
<b>17.1 Equity accounted associates and joint venture entities</b>				
SYNGENE LTD (was controlled in previous corresponding period)	42.38%	53%	14	N/A
<b>17.2 Total</b>			<b>14</b>	
17.3 Other material interests				
Axon Instruments Inc	15.79%	24.00%	-	-
Optiscan Imaging Ltd			-	-
Metabolic	10.14%	14.12%		
Pharmaceuticals Ltd	38.47%	41.40%	-	-
Amrad Corporation Ltd (from 12/5/00)	17.62%	-	-	-
<b>17.4 Total</b>			<b>-</b>	

+ See chapter 19 for defined terms.

## Issued and quoted securities at end of current period

*Description includes rate of interest and any redemption or conversion rights together with prices and dates.*

Category of +securities	Total number	Number quoted	Issue price per security (see note 14) (cents)	Amount paid up per security (see note 14) (cents)
<b>18.1 Preference +securities</b> <i>(description)</i>	-	-	-	-
18.2 Changes during current period (a) Increases through issues (b) Decreases through returns of capital, buybacks, redemptions	-	-	-	-
<b>18.3 +Ordinary securities</b>	41,038	41,038	N/A	N/A
18.4 Changes during current period (a) Increases through issues (b) Decreases through returns of capital, buybacks	5,300	5,300	\$4.50	\$4.50
<b>18.5 +Convertible debt securities</b> <i>(description and conversion factor)</i>	-	-	-	-
18.6 Changes during current period (a) Increases through issues (b) Decreases through securities matured, converted	-	-	-	-
<b>18.7 Options</b> <i>(description and conversion factor)</i>			<i>Exercise Price</i>	<i>Expiry Date (if any)</i>
	173	173	1.50	29/05/01
	18	18	1.50	01/06/02
	60	60	1.50	03/01/02
	10	10	2.00	16/09/04
	20	20	2.50	16/09/04
	20	20	2.80	16/09/04
	150	150	1.50	27/08/02
	100	100	1.00	27/08/02
	18.8 Issued during current period	775	775	6.00
18.9 Exercised during current period	100	100	1.50	12/07/00
	60	60	1.80	1/08/00
18.10 Expired during current period	-	-	-	-
<b>18.11 Debentures</b> <i>(totals only)</i>	-	-		
<b>18.12 Unsecured notes</b> <i>(totals only)</i>	-	-		

+ See chapter 19 for defined terms.

**Appendix 4B (rule 4.13(b))**  
**Half yearly/preliminary final report**

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**Comments by directors**

*Comments on the following matters are required by ASX or, in relation to the half yearly report, by AASB 1029: Half-Year Accounts and Consolidated Accounts. The comments do not take the place of the directors' report and statement (as required by the Corporations Law) and may be incorporated into the directors' report and statement. For both half yearly and preliminary final reports, if there are no comments in a section, state NIL. If there is insufficient space to comment, attach notes to this report.*

**Basis of accounts preparation**

*If this report is a half yearly report, it is a general purpose financial report prepared in accordance with the listing rules and AASB 1029: Half-Year Accounts and Consolidated Accounts. It should be read in conjunction with the last annual report and any announcements to the market made by the entity during the period. [Delete if preliminary final statement.]*

Material factors affecting the revenues and expenses of the economic entity for the current period

The economic entity experienced a decrease in operating loss before abnormal items in the current period compared to the previous half year period predominantly due to an increase in interest income, which was partly offset, by an increase in research and development. Interest income increased due to an increase in cash deposits arising from share placements.

A description of each event since the end of the current period which has had a material effect and is not related to matters already reported, with financial effect quantified (if possible)

NIL

Franking credits available and prospects for paying fully or partly franked dividends for at least the next year

NIL

Changes in accounting policies since the last annual report are disclosed as follows.

*(Disclose changes in the half yearly report in accordance with AASB 1029: Half-Year Accounts and Consolidated Accounts. Disclose changes in the preliminary final report in accordance with AASB 1001: Accounting Policies-Disclosure.)*

NIL

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+ See chapter 19 for defined terms.

## Additional disclosure for trusts

19.1	Number of units held by the management company or responsible entity or their related parties.	N/A
19.2	A statement of the fees and commissions payable to the management company or responsible entity.  Identify: <ul style="list-style-type: none"> <li>• initial service charges</li> <li>• management fees</li> <li>• other fees</li> </ul>	N/A

## Annual meeting

*(Preliminary final report only)*

The annual meeting will be held as follows:

Place	N/A
Date	N/A
Time	N/A
Approximate date the +annual report will be available	N/A

## Compliance statement

1 This report has been prepared under accounting policies which comply with accounting standards as defined in the Corporations Law or other standards acceptable to ASX (see note 12).

Identify other standards used -

2 This report, and the +accounts upon which the report is based (if separate), use the same accounting policies.

3 This report does/does not\* (*delete one*) give a true and fair view of the matters disclosed (see note 2).

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+ See chapter 19 for defined terms.

**Appendix 4B (rule 4.13(b))**  
**Half yearly/preliminary final report**

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- 4 This report is based on <sup>+</sup>accounts to which one of the following applies.  
(Tick one)
- |                                     |   |                          |   |
|-------------------------------------|---|--------------------------|---|
| <input type="checkbox"/>            | The <sup>+</sup> accounts have been audited.  | <input type="checkbox"/> | The <sup>+</sup> accounts have been subject to review.                  |
| <input checked="" type="checkbox"/> | The <sup>+</sup> accounts are in the process of being audited or subject to review. | <input type="checkbox"/> | The <sup>+</sup> accounts have <i>not</i> yet been audited or reviewed. |
- 5 If the audit report or review by the auditor is not attached, details of any qualifications are attached/will follow immediately they are available\* (*delete one*). (*Half yearly report only - the audit report or review by the auditor must be attached to this report if this report is to satisfy the requirements of the Corporations Law.*)
- 6 The entity has/does not have\* (*delete one*) a formally constituted audit committee.

Sign here: ..... Date: .....  
(Director/Company Secretary)

Print name: .....

**Notes**

- For announcement to the market** The percentage changes referred to in this section are the percentage changes calculated by comparing the current period's figures with those for the previous corresponding period. Do not show percentage changes if the change is from profit to loss or loss to profit, but still show whether the change was up or down. If changes in accounting policies or procedures have had a material effect on reported figures, do not show either directional or percentage changes in profits. Explain the reason for the omissions in the note at the end of the announcement section.
- True and fair view** If this report does not give a true and fair view of a matter (for example, because compliance with an Accounting Standard is required) the entity must attach a note providing additional information and explanations to give a true and fair view.
- Consolidated profit and loss account**
  - Item 1.1 The definition of "revenue" and an explanation of "ordinary activities" are set out in *AASB 1004: Revenue*, and *AASB 1018: Statement of financial performance*.
  - Item 1.6 This item refers to the total tax attributable to the amount shown in item 1.5. Tax includes income tax and capital gains tax (if any) but excludes taxes treated as expenses from ordinary activities (eg, fringe benefits tax).
- Income tax** If the amount provided for income tax in this report differs (or would differ but for compensatory items) by more than 15% from the amount of income tax *prima facie* payable on the profit before tax, the entity must explain in a note the major items responsible for the difference and their amounts.

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+ See chapter 19 for defined terms.

5. **Consolidated balance sheet**

**Format** The format of the consolidated balance sheet should be followed as closely as possible. However, additional items may be added if greater clarity of exposition will be achieved, provided the disclosure still meets the requirements of *AASB 1029: Half-Year Accounts and Consolidated Accounts*, and *AASB 1040: Statement of Financial Position*. Banking institutions, trusts and financial institutions identified in an ASIC Class Order dated 2 September 1997 may substitute a clear liquidity ranking for the Current/Non-Current classification.

**Basis of revaluation** If there has been a material revaluation of non-current assets (including investments) since the last <sup>+</sup>annual report, the entity must describe the basis of revaluation adopted. The description must meet the requirements of *AASB 1010: Accounting for the Revaluation of Non-Current Assets*. If the entity has adopted a procedure of regular revaluation, the basis for which has been disclosed and has not changed, no additional disclosure is required. Trusts should also note paragraph 10 of *AASB 1029* and paragraph 11 of *AASB 1030: Application of Accounting Standards etc.*

6. **Consolidated statement of cash flows** For definitions of “cash” and other terms used in this report see *AASB 1026: Statement of Cash Flows*. Entities should follow the form as closely as possible, but variations are permitted if the directors (in the case of a trust, the management company) believe that this presentation is inappropriate. However, the presentation adopted must meet the requirements of *AASB 1026*. <sup>+</sup>Mining exploration entities may use the form of cash flow statement in Appendix 5B.

7. **Net tangible asset backing** Net tangible assets are determined by deducting from total tangible assets all claims on those assets ranking ahead of the <sup>+</sup>ordinary securities (ie, all liabilities, preference shares, outside <sup>+</sup>equity interests etc). <sup>+</sup>Mining entities are *not* required to state a net tangible asset backing per <sup>+</sup>ordinary security.

8. **Gain and loss of control over entities** The gain or loss must be disclosed if it has a material effect on the <sup>+</sup>accounts. Details must include the contribution for each gain or loss that increased or decreased the entity’s consolidated profit (loss) from ordinary activities and extraordinary items after tax by more than 5% compared to the previous corresponding period.

9. **Rounding of figures** This report anticipates that the information required is given to the nearest \$1,000. However, an entity may report exact figures, if the \$A’000 headings are amended. If an entity qualifies under ASIC Class Order 98/0100 dated 10 July 1998, it may report to the nearest million dollars, or to the nearest \$100,000, if the \$A’000 headings are amended.

10. **Comparative figures** Comparative figures are the unadjusted figures from the previous corresponding period. However, if there is a lack of comparability, a note explaining the position should be attached.

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<sup>+</sup> See chapter 19 for defined terms.

**Appendix 4B (rule 4.13(b))**  
**Half yearly/preliminary final report**

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11. **Additional information** An entity may disclose additional information about any matter, and must do so if the information is material to an understanding of the reports. The information may be an expansion of the material contained in this report, or contained in a note attached to the report. The requirement under the listing rules for an entity to complete this report does not prevent the entity issuing reports more frequently. Additional material lodged with the +ASIC under the Corporations Law must also be given to ASX. For example, a directors' report and declaration, if lodged with the +ASIC, must be given to ASX.
12. **Accounting Standards** ASX will accept, for example, the use of International Accounting Standards for foreign entities. If the standards used do not address a topic, the Australian standard on that topic (if one) must be complied with.
13. **Corporations Law financial statements** As at 1/7/96, this report may be able to be used by an entity required to comply with the Corporations Law as part of its half-year financial statements if prepared in accordance with Australian Accounting Standards.
14. **Issued and quoted securities** The issue price and amount paid up is not required in items 18.1 and 18.3 for fully paid securities.
15. **Relevant Items** AASB 1018 requires the separate disclosure of specific revenues and expenses which are not extraordinary but which are of a size, nature or incidence that disclosure is *relevant* in explaining the financial performance of the reporting entity. the term "relevance" is defined in AASB 1018. For foreign entities, there are similar requirements in other accounting standards normally accepted by ASX.
16. **\$ Dollars** If reporting is not in A\$, all references to \$A must be changed to the reporting currency. If reporting is not in thousands of dollars, all references to "000" must be changed to the reporting value.

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+ See chapter 19 for defined terms.

## **CIRCADIAN TECHNOLOGIES LIMITED AND CONTROLLED ENTITIES**

### **DIRECTORS' REPORT**

The Board of Directors of Circadian Technologies Limited ("Circadian") has pleasure in submitting its report in respect of the financial half year ended 31 December 2000.

#### **Directors**

The names of the directors in office during or since the end of the half year are:

Sir Peter J Derham (Chairman)  
Leon Serry (Managing Director)  
Ian R Davis  
Professor Ray L Martin  
Dr John Stocker

Unless otherwise indicated, all directors held their position as a director throughout the entire half year and up to the date of this report.

#### **Principal Activities**

The principal activities of the consolidated entity include the management and funding of pharmaceutical research and development projects with Australian and New Zealand Universities to the stage where collaborative and/or licensing arrangements with major international pharmaceutical companies are sought. These activities also include investment in leading edge Australian technology. The consolidated entity is committed to the innovation, management and commercialisation of its projects and technology investments.

#### **Results**

The consolidated loss of the consolidated entity for the half year was \$592,600 (1999: \$810,635) after income tax of nil (1999: nil).

#### **Review of Operations**

In July 2000, Circadian completed a share placement of 5,300,000 ordinary shares at an issue price of \$4.50 per share for the purpose of providing working capital to fund development of technology and investment in technology related projects and opportunities. This increased the company's share capital by \$22,913,663 (net of directly related costs on the issue of equity) to \$49,718,710.

The economic entity experienced a decrease in operating loss before abnormal items in the current period compared to the previous half year period predominantly due to an increase in interest income, which was partly offset, by an increase in research and development.

Detailed below is an update on the consolidated entity's interests in listed technology holdings and research and development projects for the half year ended 31 December 2000. The 30 June 2000 annual report contains detailed background information relating to these holdings and projects.

**Metabolic Pharmaceuticals Limited – Advanced Obesity Drug and Type II Diabetes Projects**

***Circadian Holding - Market Value 31 December 2000: \$28.08 million; Book value: \$Nil***

***Shareholders: Circadian: 38.5%; Monash: 25.6%; Others: 35.9%***

Metabolic Pharmaceuticals Limited (“Metabolic”) has advised the following through their public announcements:

- AOD9604 Obesity Drug: Pre-clinical toxicology tests of compound AOD9604 were successfully completed and the Ethics Review Board at Medeval, Metabolic’s UK Clinical Trials Contractor, “has given its approval for the conduct of Metabolic’s planned Phase I human clinical trial of the obesity drug”.

Dosing of the first volunteer is expected to begin around 7 February 2001 and the trial, to be conducted with a total of 16 volunteers, is expected to be completed about 12 April with results available shortly thereafter.

- Veterinary Applications of AOD9604: As previously advised, Metabolic is assessing the potential veterinary applications of the AOD technology, and is initially investigating its application to reduction of back fat in pigs.

Metabolic now has small quantities of a prototype food additive produced under contract at CSIRO, which on preliminary investigation appear to contain useful quantities of AOD. Further laboratory analysis is under way.

- In December SemBioSys executed a funded feasibility study agreement with Metabolic. Under the terms of the agreement, SemBioSys will evaluate the feasibility of producing Metabolic’s proprietary anti-obesity peptide AOD9604 using SemBioSys’ patented oil body/oleosin protein production platform.

If the clinical trials of Metabolic’s obesity drug AOD9604 are successful, multi-tonne quantities of pharmaceutical grade AOD9604 will need to be produced at low cost. Metabolic believes that the SemBioSys process has the greatest potential to meet these requirements.

SemBioSys is a Calgary-based biotechnology company focused on the development of high value protein and oil body based products using its proprietary oil body/oleosin technology. The company was spun out of the University of Calgary in 1996.

Metabolic’s half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

**Axon Instruments Inc (USA) - Developers and manufacturers of genomics and bio-informatics products**  
**- World Market Leader in Instrumentation and Software for Cellular Electrophysiology**

***Circadian Holding – Market Value 31 December 2000: \$101.5 million; Book Value: \$1.4 million***

***Shareholders: Circadian: 15.8%; Others: 84.2%***

Highlights from Axon Instruments Inc (“Axon”) shareholder update released on 2 November 2000:

- In July, Axon signed an agreement with the CSIRO for the development of advanced bioinformatics and imaging algorithms which will be relevant for its products Javelin (bioinformatics software that manages and analyses the large amounts of data produced by microarray scanners such as GenePix) and CellPix (optically scans a multi-well plate to measure the effects of many different drug candidates on biological materials in the wells).
- In August, Axon completed a placement of 39,062,500 ordinary shares at an issue price of \$1.28 per share to raise a total of \$50 million. The purpose of the placement was to fund the commercialisation and acquisition of intellectual property for next generation cell-based screening, and proteomics; research and development of consumables for proteomics and cell-based screening products.
- Axon recently signed an exclusive worldwide license agreement and research collaboration with Yale University (US) for a revolutionary high-throughput patch clamp technology. Axon will fund ongoing research into the technology at Yale University, and has secured the rights to downstream technology developed from the research. Axon plans to use this technology as the core component in a device (known as RoboPatch) for screening pharmaceutical agents acting on mammalian cell-membranes ion-channels and transporters. Ion channel activity is important for studying many medical disorders, including migraine, epilepsy, irregular heartbeat and cystic fibrosis.

Currently, pharmaceutical screening of important ion-channel drugs is inefficient because the techniques are indirect. Axon's device has the potential to resolve a major bottleneck in the drug discovery process.

- In August, Roche Biosciences, part of Roche Pharmaceuticals Research, joined Axon's consortium for the development of RoboClamp (a high throughput electrophysiology screening system to be mostly used in the drug discovery market). Roche has extensive experience in high throughput screening, and Axon expects them to provide valuable product evaluation.
- In October, the Parke-Davis division of Pfizer joined Axon's consortium for the development of CellPix. Parke-Davis joins existing members AstraZeneca, Geron Corp and Cytokinetics.

Axon's annual report for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

#### **Optiscan Imaging Limited - Early Cancer Detection**

***Circadian Holding - Market Value 31 December 2000: \$11.02 million; Book value: \$361,132***

***Shareholders: Circadian: 10.1%; Axon: 15.4%; Others: 74.5%***

Optiscan Imaging Limited ("Optiscan") has advised the following in their annual report released in October 2000 and in their public announcement dated 16 January 2001:

- **Hand Held Probe** (Annual Report)  
The release of the hand held probe is impending. Optiscan anticipates that uptake by the conservative medical marketplace will remain modest in the short to medium term. During this time, Optiscan will engage in significant market development activity, focusing on the support of early adopters and medical opinion leaders in their use of the probes. This will be aimed at ensuring that the growing realm of uses is realised in clinical practice, increasing the appeal of the product to the broader dermatological community. Achievement of substantial market penetration as a result of this process

is likely to result over a two to three year period. As such, Optiscan will continue to be associated with multiple trials well beyond the actual release of the product.

- **Flexible Probe** (Annual Report)

Progress has continued to be made in miniaturisation of scanning mechanisms for the flexible probe. This project is on track to construct advanced prototype probes for clinical trial in the 2001 calendar year.

Potential applications in gastroenterology include: colon cancer, mouth cancer, gastric cancer, Barrett's oesophagus, ulcerative colitis and cancer management.

In parallel with the probe development, animal studies have been conducted to investigate several of these applications. With the use of several human-safe contrast agents, results of these investigations have been very encouraging.

- **Alliances** (Annual Report)

Discussions with potential strategic allies and partners are continuing. The possibility exists for multiple partnering relationships including those associated with technology relating to consumables and telemedicine.

- **US FDA Update** (16 January 2001 ASX Announcement)

Optiscan has lodged its submission to the US Food & Drug Administration to distribute its optical-fibre microscopes in the USA. Mr Delaney confirmed that it was not unusual for the FDA to take several months before giving an answer.

According to Optiscan's Managing Director, Optiscan's product faces low regulatory barriers because it is not hazardous to patients, it is not implanted and therefore does not come into contact with internal tissue, and the instrument does not make diagnostic decisions on behalf of clinicians. Traditionally, the FDA looks favourably on such products.

Optiscan technology has been used for research purposes in the US for several months including at the prestigious Centre for Biologic Imaging at the University of Pittsburgh. Optiscan's Managing Director said: "Optiscan plans to widen its clinical trials this year to include its second product, which is for gastroenterology. The company is presently making pleasing and positive headway with its skin cancer trials."

Optiscan's half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

### **Syngene Limited - Gene Diagnostics**

**Shareholders:** *Circadian: 42.4%; Casthree Pty Ltd: 20%; Howard Florey Institute: 19.5%; Howard Florey Institute staff and others: 18.1%*

- Negotiations are continuing with a major US medical diagnostic company, which may require a non-exclusive worldwide license in respect of one of Syngene's patents in the area of in situ hybridization. In situ hybridisation locates precise gene activity in sections of tissue and caters to diagnostic markets. The market for DNA therapeutics and diagnostics is expected to show substantial growth especially in light of the recent completion of the first draft map of the Human Genome. The patent was granted in the US in 1997, providing Syngene with 17 years protection to

2014 in the US. Patents have also been granted in Europe, Canada, Japan and Australia.

- Polychip's interest was diluted to 42.4% as a result of an issue of shares to Castthree Pty Ltd (a subsidiary of Consolidated Press Holdings Limited).

### **Antisense Therapeutics Limited - Gene Directed Therapeutics**

- Antisense Therapeutics Limited ('ATL') was incorporated on 13 November 2000 to develop antisense technologies.
- Antisense cell therapy relates to the field of gene therapy whereby synthetic genetic material may be used to block the action of genes that produce disease-causing proteins. A possible advantage of antisense drugs over conventional drugs is that antisense has the potential to be rationally designed with acknowledge of the genetic target, whereas conventional drugs are found typically by a process of extensive trial and error. Interest in antisense technologies has been fuelled by the rapid growth and understanding of the science of genomics (including the Human Genome Project, which provides a source of gene sequence data for rational drug design using antisense). ATL is presently formulating several innovative projects, which relate to the use of antisense technology and potential collaborations in this area are in the process of negotiation.

Further capital will be required in the forthcoming period for these antisense activities and consequently a listing may be sought on the Australian Stock Exchange, the precise timing of which will depend on the progress of the projects and collaborations relating to these expanded activities.

### **AMRAD Corporation Limited**

*Circadian Holding - Market Value 31 December 2000: \$17.5 million; Book value: \$16.6 million*

*Shareholders: Circadian: 17.6%; Others: 82.4%*

- Circadian's wholly owned controlled entity Fibre Optics (Aust) Pty Ltd increased its holding in AMRAD Corporation Limited ("AMRAD") from 10% at 30 June 2000 to 17.6% at period end. Since 31 December 2000 the holding has increased to 19.12%.
- AMRAD is a listed biotechnology research and development company and is one of Australia's oldest biotechnology companies established by the Victorian Government and four Melbourne based medical institutions in 1986, eventually listing in 1996. AMRAD was founded to commercialise medical discoveries from Victorian research institutions.

AMRAD's half-year financial statements for 31 December 2000 and related ASX announcements should be read in conjunction with this report for further information.

### **Meloma Pty Ltd - Cancer Diagnostic/Therapeutics**

*Shareholders: Circadian: 30%; Inventors and Others: 70%*

- On 8 December 2000 Fibre Optics (Aust) Pty Ltd, a wholly owned subsidiary of Circadian, together with the inventing scientists incorporated Meloma Pty Ltd with Fibre Optics providing \$400,000 for research funding.

Meloma has the rights (patent application) to a novel method for rapid identification and detection of

cancer-specific antigens. The methodology may have applications for a broad range of cancers, including breast, ovarian, colorectal and prostate cancers. A provisional patent application covering the technology has been lodged.

Researchers are being appointed for the development of new blood tests for cancer detection, which may also have potential for new therapeutic products. It is expected that the first phase of the research programme will be completed later this calendar year.

The market for cancer tests is substantial and current tests in most cases are unsatisfactory.

### **Cancer Research Projects - XR5000**

*Circadian interest: 16.67% of any scheduled milestone payments and royalties of 2% of sales made by Xenova*

Highlights from Xenova Plc's ("Xenova") public announcements for the period:

#### **XR5000 Phase II Human Clinical Trials**

- Xenova raised £10 million in a public offer during the period. Part of the proceeds will be applied towards the completion of Phase II clinical trials and, if appropriate, together with a partner, conducting Phase III trials for XR5000.
- Phase II human clinical trials for ovarian, non-small lung and glioma cancers are in progress. Final data from these three remaining studies are expected to be available shortly. Results from these trials will help determine the future development strategy for this compound.

#### **XR5000 Second Generation Drug Leads**

- A patent application has been made relating to XR5000 second generation drug leads. This includes XR5944, which is part of this family of drug leads.

### **Gene Directed Enzyme Prodrug Therapy Technology Project 'GDEPT' – Cancer Research Project**

*Circadian: entitled to 30% of net income due to Auckland Division Cancer Society of New Zealand Inc ('Society')*

#### ***Background:***

An agreement was signed on 10 April 1996 between Circadian and the Society in relation to the GDEPT project, whereby Circadian is entitled to 30% of all royalties and milestones and any other entitlements due to the Society.

Most anticancer drugs are cytotoxic agents, which distribute widely in the body and selectively kill dividing cells (rather than only cancer cells). Such drugs are limited in their efficacy by the necessity to restrict the damage they cause to rapidly dividing normal cells. To achieve further substantial improvements in efficacy, more selective approaches are required. One is to use non-toxic prodrug forms of cytotoxic agents, and activate these selectively in tumours. This can be achieved in principle by incorporating a non-human gene into the tumour cells, so that these cells selectively produce a non-human enzyme that is able to activate the prodrug (a drug that requires further metabolism before becoming biologically active). Prodrugs suitable for this approach must be non-toxic, and able to be activated selectively only by the chosen non-human enzyme to release a very potent cytotoxin. Vion Pharmaceuticals Inc, Onyx Pharmaceuticals Inc and AstraZeneca are involved in the project. Circadian has no further funding commitments relating to this project.

### **Analgesic Project - Non-Sedating Analgesics**

*Project Owners: Circadian: 85.7%; Monash University: 14.3%*

- Ongoing development and testing has continued during the period at Monash University and at an independent laboratory with the aim of selecting a lead compound for analgesic use from which options for further commercialisation will be explored.
- Circadian extended the funding for the project by an additional 3 months to March 2001. The additional funding amounts to \$21,890.

### **Yeast Mediated Reactions Project (Ephedrine)**

*Project Owners: Circadian: 60%; Victoria University of Technology: 40%*

- Work is continuing on the new method of producing ephedrine. Circadian is now funding the second phase of the project for a further 12 month period to 1 October 2001, in accordance with the original research and development agreement. The funding amounts to \$51,000 for research and development plus \$54,000 for equipment.
- Circadian's interest in the project increased from 50% to 60% during the period under review.

### **Circadian Rhythm Disorders Project**

*Project Owners: Circadian: 60%; Monash: 40%*

- Eli Lilly and Company ("Lilly") have a non-exclusive worldwide license in respect of the patents and negotiations are being conducted at present with several parties regarding licensing the further development of Lilly's melatonin analogue to complete more definitive phase II human studies. The analogue has been studied by Lilly in two early Phase II studies.

For and on behalf of the Board:

Leon Serry  
Director

Professor Ray Martin  
Director

Melbourne  
30 January 2001

**CIRCADIAN TECHNOLOGIES LIMITED AND CONTROLLED ENTITIES**

(A.C.N. 006 340 567)

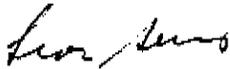
**DIRECTORS' DECLARATION**

The Directors declare that:

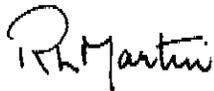
- (a) the financial statements and associated notes comply with the accounting standards and Urgent Issues Group Consensus Views;
- (b) the financial statements and notes give a true and fair view of the financial position as at 31st December 2000 and performance of the consolidated entity for the half-year then ended; and
- (c) in the Directors' opinion, there are reasonable grounds to believe that the Company will be able to pay its debts as and when they become due and payable.

Made in accordance with a resolution of Directors.

For and on behalf of the Board.



Leon Serry  
Director



Professor Ray Martin  
Director

Melbourne  
30th January, 2001.

**Independent Review Report**

To the Members of  
Circadian Technologies Limited

**Scope**

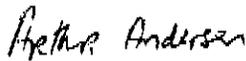
We have reviewed the financial report of Circadian Technologies Limited for the half-year ended 31 December 2000, as set out on pages 8 to 13. The financial report includes the consolidated financial statements of the consolidated entity comprising the company and the entities it controlled at the end of the half-year or from time to time during the half-year. The company's directors are responsible for the financial report. We have performed an independent review of the financial report in order to state whether, on the basis of the procedures described, anything has come to our attention that would indicate that the financial report is not presented fairly in accordance with Accounting Standard AASB 1029 "Interim Financial Reporting", other mandatory professional reporting requirements and statutory requirements in Australia so as to present a view which is consistent with our understanding of the consolidated entity's financial position, and performance as represented by the results of its operations and its cash flows, and in order for the company to lodge the financial report with the Australian Securities and Investments Commission.

Our review has been conducted in accordance with Australian Auditing Standards applicable to review engagements. The review is limited primarily to inquiries of the company's personnel and analytical procedures applied to the financial data. These procedures do not provide all the evidence that would be required in an audit, thus the level of assurance provided is less than given in an audit. We have not performed an audit and, accordingly, we do not express an audit opinion.

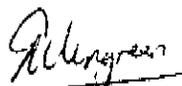
**Statement**

Based on our review, which is not an audit, we have not become aware of any matter that makes us believe that the half-year financial report of Circadian Technologies Limited is not in accordance with:

- (a) the Corporations Law, including:
  - (i) giving a true and fair view of the consolidated entity's financial position as at 31 December 2000 and of its performance for the half-year ended on that date; and
  - (ii) complying with Accounting Standard AASB 1029 "Interim Financial Reporting" and the Corporations Regulations; and
- (b) other mandatory professional reporting requirements.



Chartered Accountants



Partner  
Melbourne  
30 January 2001