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Cevira CL7 Device: Engineering Design Specification

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Authored by: Tore Gjørsvik Medical Device Director, Photocure	**Date:** 13.05.2015
Approved by: Gry Stensrud VP Technical Development and Operations, Photocure	**Date:** 13.05.2015
Approved by: Anne Gautvik Horten RA Director (consultant), Photocure	**Date:** 13.05.2015
Authorized by: Anne Wallin Quality Director, Photocure	**Date:** 13 May 2015

Revision History

Rev.	Issue Date	Prepared by	Authorized by	Reason/Description
01	07/10/2009	Mike Cox	Mike Cox	Initial release
02	23/03/2010	Mike Cox	Mike Cox	Update at end of phase 2
03	10/08/2010	Mike Cox	Mike Cox	Update at end of phase 3
04	19/05/2011	Mike Cox	Mike Cox	Section 2 - Changes to illumination sequence for software v1.1.4 incorporated Section 3.3 – correction to power dissipation. Section 6.2 – updated assembly diagram added Section 6.3 – requirement for sterilisation removed Section 8.1.2 – ratification status of IEC 60601-1 removed
05	28/05/2013	Euan Morrison	Jo Morgan	General update for Phase 3 clinical trial device design • 4.2.1 Updated for LED binning • 4.2.4 Remove reference to over moulding • 6.2 update mechanical construction to reflect Phase 3 clinical trial device design • 6.3 lens material changed to MED4940 • 6.3 remove primer and change adhesive to MED3 • 7.1 update to include Nolato as moulder and final device assembler • 8.1.2 Update to refer to IEC 60601-1 3rd edition
06	08/05/2015	Tore Gjørsvik	Anne Wallin	Further update for Phase 3 clinical trial device design. • 1.1 Total treatment time set to 11 hrs. • 1.2 Updated Intended Use. • 6.3 Added string to materials • 7. Updated production sequence. Editorial changes to update supplier information. • 8.1.2 Revised section in accordance with IEC60601-1 • 8.1.3 Added info on biocompatibility • 8.2 Added requirements for disposal in US. • Figure 2 Corrected in line with changes in version 5.

Contents

1 Product Overview

1.1 Product Description

The Cevira CL7 device is a single-use disposable device used to provide photo dynamic treatment (PDT) of the cervix in women with cervical intraepithelial neoplasia (CIN).

The device forms one part of a drug-device combination therapy and combines delivery of the drug formulation to the cervix and photo-activation of accumulated photoactive porphyrins, protoporphyrin IX (PpIX) using a LED-based light source contained within the device

The device is self-contained and self-powered and is intended to be fitted inside the vaginal cavity in contact with the cervix for a period of several hours during which time the therapy is delivered. The treatment procedure is as follows:

- Device is fitted to the cervix by a gynaecologist.
- The cup in the device is used to hold the drug (ointment) against the cervix for an initial absorption period of several hours
- A light source integrated into the cup and matched to the absorption wavelength required for photo-activation of the drug is automatically activated and delivers the required light dose to provide the therapy.
- The patient removes the device when the treatment is completed, minimum after 11 hours.

The requirements in this document are based on a device with these characteristics.

The system-level requirements for the product are detailed in the latest version of the Cevira CL7 Device Product Requirements Specification (ref KLEM_DI04_0001)

1.2 Intended Use

Cevira is indicated for treatment of biopsy-confirmed cervical High-grade Squamous Intraepithelial Lesions, HSIL (CIN2 and CIN3) in subjects 18 years and older.

1.3 Product Volumes

It is anticipated that approximately 2000 units will be fabricated for the Phase 3 trials.

1.4 Product Variants

A single 'average size' product configuration will be produced. No other variants will be produced.

1.5 Manufacturing

The Phase 3 clinical trial units will be produced under controlled conditions by a ISO13485 certified contract manufacturer (Nolato AB, Torekov, Sweden). The manufacture will also be in compliance with 21CFR820 and the European medical device directive, 93/42 EEC. Devices will be manufactured clean and within microbiological quality requirements as defined by Photocure.

2 Mode of Use

During normal use the Cevira CL7 Device will progress through a number of lifecycle states spanning the pre-treatment, treatment and post-treatment stages of use.

State	Description	Duration
Pre-treatment phase		
WAIT state	Device removed from packaging and fitted to patient by clinician Green indicator LED flashes ON/OFF with 50/50duty cycle to provide 'heart beat'	15 minutes
ABSORB state	Device goes into a stand-by state (post fitting) to await absorption of pharmaceutical prior to initiating illumination of treatment LEDs. Red treatment LEDs and green indicator LED flash to provide 'heart beat'	5 hours
Treatment phase		
ILLUMINATE state	Treatment LEDs are illuminated to provide the photo-dynamic therapy	Long enough to deliver > 50J/cm^2 over surface of cervix (4.6 hours)
Post-treatment phase		
NOTIFY state	Device signals success/error status when device is removed. Green indicator LED signals success. Red treatment LEDs signal failure.	Until battery volts drop below acceptable level (2.5V)
SHUTDOWN state	Battery volts drops below acceptable level (2.5V) and micro is placed into a 'safe' mode of operation	Until micro unable to operate and/or battery completely exhausted
EXHAUSTED state	Battery exhausted	

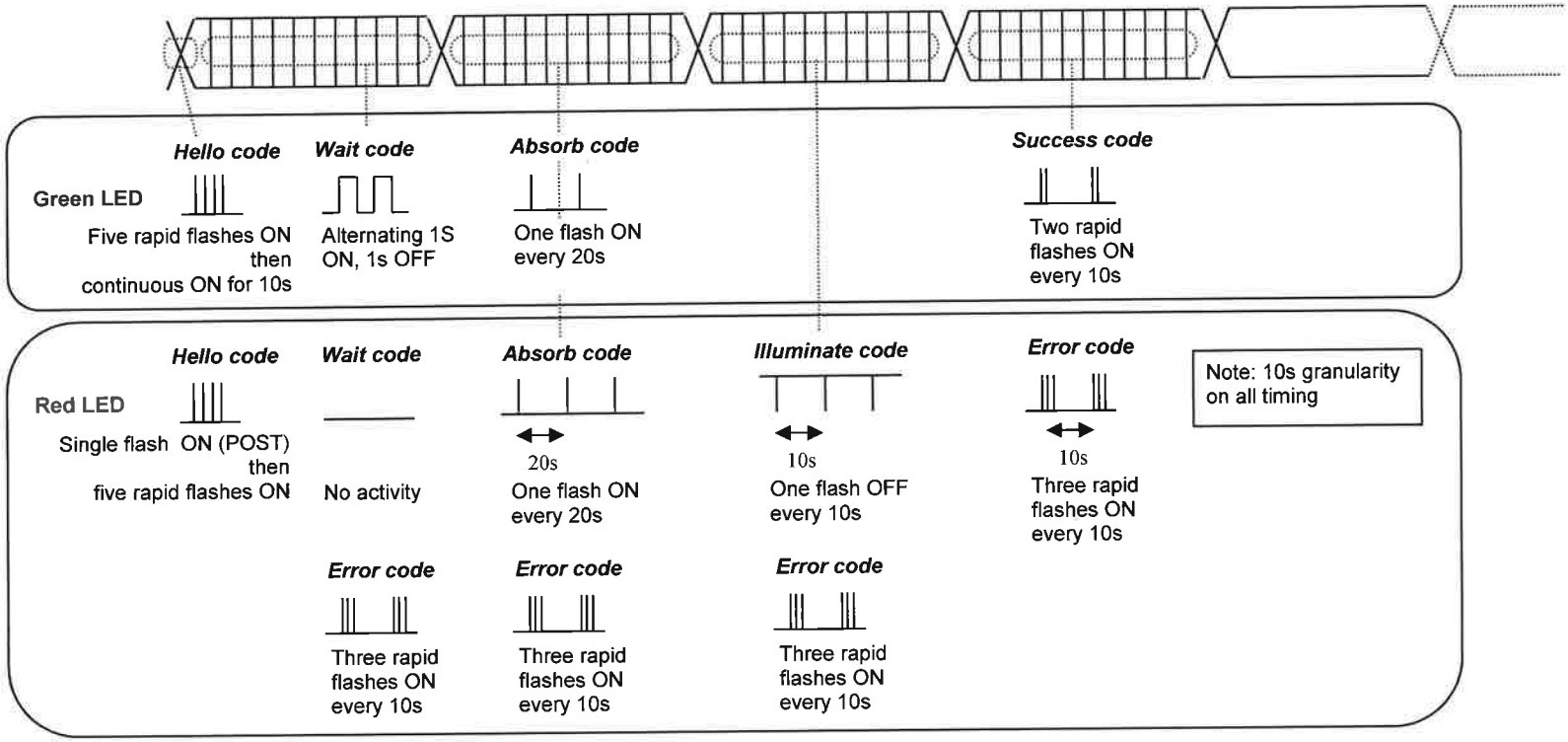
There are two further factory test modes that can be used during production of the device:

- BOARD TEST mode – used to test the PCB prior to device assembly
  - Activated by asserting correct logic level on two programming/test interface pins when device powered up
- DEVICE TEST mode – final assembly test for the completed device
  - Activated by toggling (replace and remove) magnet three times with period between toggles not exceeding 10s. Device test mode entered when magnet is removed for 4th time.

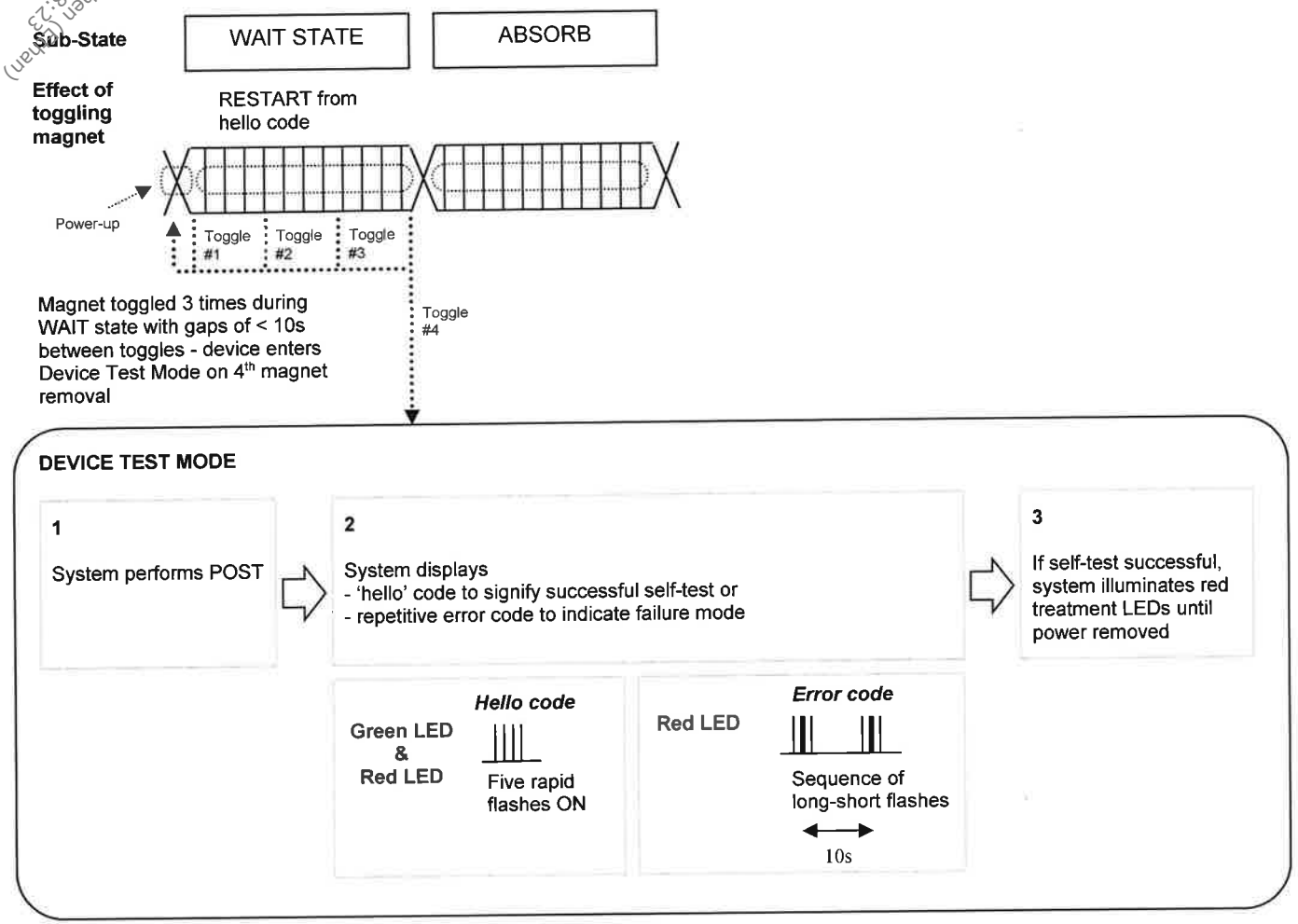
The following diagrams illustrate device operation in normal use (treatment mode) and in device test mode, including usage of the red treatment and green indicator LEDs during the various stages of treatment

TREATMENT MODE

State	Pre-treatment		Treatment	Post-treatment		
Sub-State	WAIT STATE	ABSORB	ILLUMINATE	NOTIFY	SHUTDOWN	EXHAUSTED
Effect of toggling magnet	RESTART from beginning hello code	CONTINUE from interruption	CONTINUE from interruption	CONTINUE from interruption	CONTINUE from interruption	
Duration	TBD	~ 5 hours	~ 4.6 hours	Undefined		



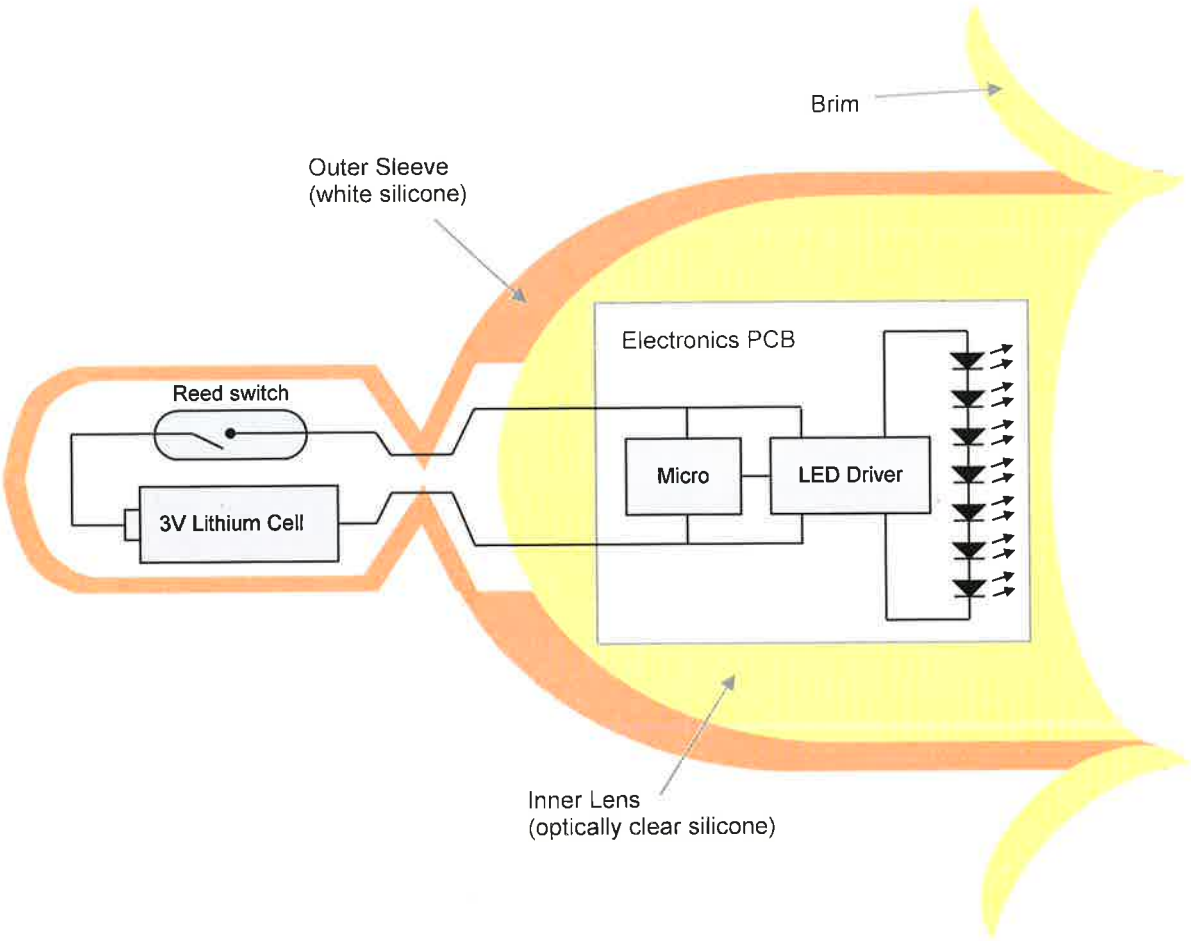
DEVICE TEST MODE



3 System Architecture

3.1 Overall Architecture

The overall system architecture of the Cevira CL7 Device is illustrated in the following diagram:



The principal component parts of the Cevira CL7 Device are:

- An electronics PCB assembly containing
  - seven red LED treatment LEDs
  - a LED driver circuit incorporating a step-up DC/DC converter
  - a microcontroller with software that sequences and monitors the device operation
- A transparent silicone lens that
  - provides a smooth concave inner surface that conforms to the surface of the cervix
  - includes an outer brim that conforms with the vaginal wall and helps to locate the device
- A cylindrical 3V primary non-rechargeable Lithium cell
- A magnetically-activated reed switch to enable/disable the battery power
- A white silicone outer sleeve that
  - provides a rear tail with cavity for the Lithium cell and reed switch

3.2 Optical Configuration

3.2.1 LED configuration

The Cevira CL7 Device will contain 7 high brightness Luxeon Rebel LEDs mounted in a hexagonal arrangement on a flat PCB. The LEDs will be mounted on a flat PCB with a single LED in the centre and the remaining 6 LEDs arranged equidistant from the central LED in a regular hexagon. The LED spacing will be set to 11mm. This arrangement enables a relatively uniform light distribution to be produced on the cervix .

Figure 1 shows a cross section through the Cevira CL7 Device optics showing the relative position of the LED emitter plane to the spherical Cevira CL7 Device illumination surface. Also shown is the hexagonal arrangement of the LEDs as seen through the Cevira CL7 Device aperture.

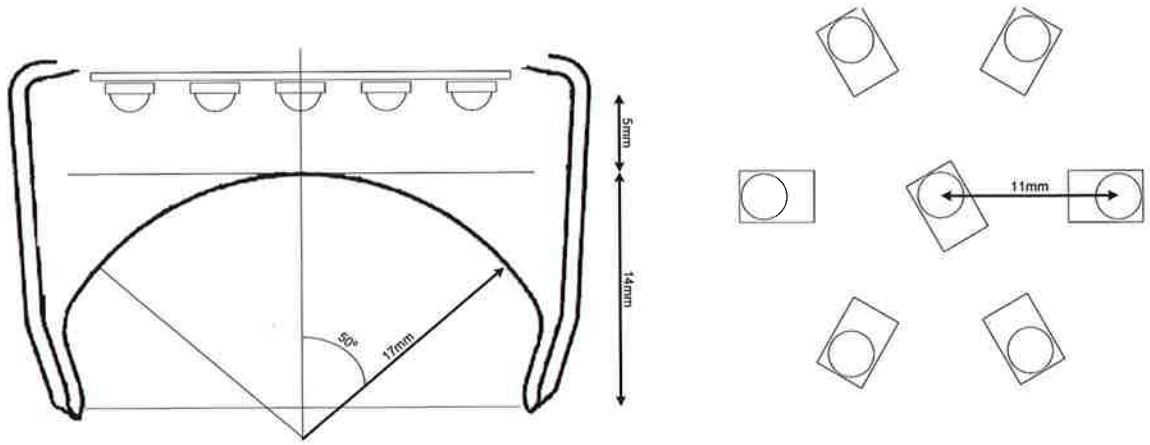


Figure 1: Left: Cross section through Cevira CL7 showing position of LED emitter plane relative to spherical Cevira CL7 surface. Right: Hexgonal arrangement of LEDs as viewed from cap aperture.

The specific arrangement of the LED emitters and spacing from the spherical Cevira CL7 Device surface is designed to optimise the light distribution from the LEDs.

The LEDs will be embedded in a soft, clear, silicone enabling high transmission of the light emitted by the LEDs towards the cervix.

3.2.2 Active area

From Figure 1 it can be seen that the spherical illumination surface of the Cevira CL7 Device extends to a maximum cone angle of ~124 degrees. However at the extremes of the illumination area, the irradiance levels will be relatively low and variable and dependent on manufacturing tolerances. In addition at cone angles beyond 50 degrees the irradiance levels produced by the Cevira CL7 Device become difficult to measure because of the tapered profile which has been designed to ensure a good fit to the cervix.

As a result, the active area of the device has been defined as the area subtended by the 100 degree cone angle shown in Figure 1. This represents over 70% of the illumination surface of the Cevira CL7 Device.

3.2.3 Device irradiance

Using the LED geometry described in section 3.2.1, the Cevira CL7 device will produce an irradiance profile similar to that shown below in Figure 2. The "in line" profile is measured along a diameter that includes the central LED and two outer LEDs while the "across" profile is measured along a diameter that passes mid-way between LEDs in the outer ring (but includes the central LED).

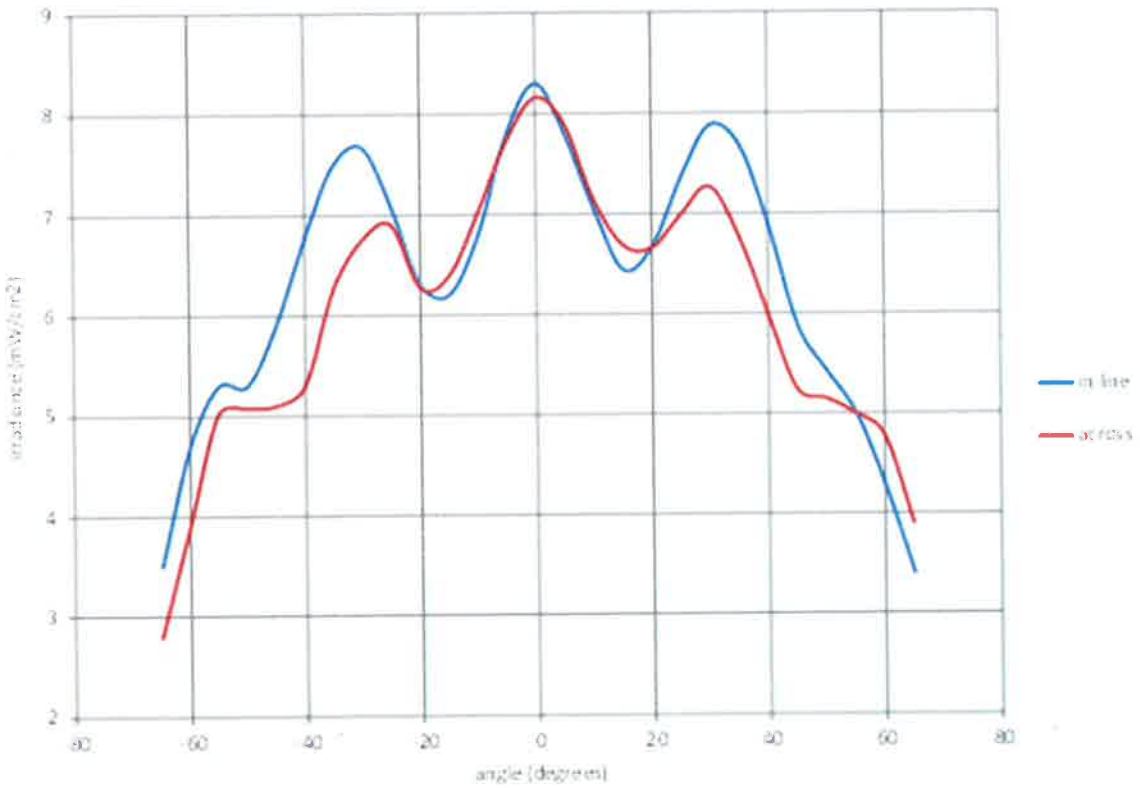


Figure 2: Cevira CL7 Device irradiance profile

The irradiance levels shown in Figure 2 is typical for the device and will be achieved under the following conditions:

- Luxeon Rebel LEDs from the H4W bin
- LED drive level of ~20mA
- Central LED power level reduced by 50%
- LED emitting plane ~5.5mm from apex of spherical Cevira CL7 Device surface

Under these conditions ~325mW of power will be delivered to the device – 260mW of which will be dissipated by the LEDs (~75% heat, 25% light) and 65mW in the electronics.

3.3 Thermal Performance

To achieve the irradiance profile shown in Figure 2, the LED drive current will be set to ~20mA. Under these conditions, the forward voltage of the 7 LED chain will typically be 14V (this assumes the LEDs will be selected from the W voltage bin – see section 4.2.1). The total power dissipated in the LEDs will be ~260mW, of which ~75% will be dissipated as heat through the LED case and ~25% as light.

The total power dissipated in the Cevira CL7 Device under these conditions will be ~325mW (assuming the LED driver is ~80% efficient – see section 4.2.3).

Thermal modelling of the Cevira CL7 device has indicated that dissipating 325mW through the LEDs alone results in a peak temperature of <43.0 ºC at the apex of the Cevira CL7 Device. The temperature limit set by IEC60601 to avoid a burn hazard (see section 8.1.2) is 43ºC.

3.4 Dose Model

The Cevira CL7 Device is designed to deliver a light dose of >50J/cm^2 over the active area of the device. Referring to Figure 2 which shows the typical device irradiance, it can be seen that for a cone angle of ±50° (the defined active area of the device), the irradiance exceeds 3mW/cm2. Assuming that this irradiance level remains constant throughout the treatment time, a dose of >50J/cm^2 will be delivered across the active area with a treatment time of 4.6 hours.

Table 1 gives an indication of the light dose levels which can be delivered as a function of treatment time and irradiance level.

irradiance mW/cm^2	dose J/cm^2, 2.8 hours	dose J/cm^2, 4.6 hours
3	30	50
5	50	83
9	90	149
12	121	198

The effectiveness of the treatment is dependent not only on the light dose delivered, but also the spectral characteristics of the light used in the treatment. Previous Photocure products – the CL128 & CL512 lamps - use a dose factor to normalise the light dose delivered to that of a standardised LED which has a peak wavelength of 635nm and a FWHM of 21nm (the Even's LED) and its overlap with the PPIX excitation spectrum. Also taken into account is the variation in time of the light source.

The Cevira CL7 device will be used with relatively low LED drive currents and as a result its thermal performance will be relatively stable over time. The irradiance levels and spectral characteristics of the light source will not vary significantly over time (<1%) and as a result, the dose which is delivered by the device will be linearly proportional to the treatment time.

In comparing the Cevira CL7 Device to the standard Even's LED, there are two factors to take into account: LED peak wavelength and FWHM. Figure 3 shows the spectrum of light emitted by the LEDs used in the Cevira CL7 Device compared to the PPIX excitation spectrum. As can be seen, the Cevira CL7 Device LEDs are slightly short of the PPIX peak, but the spectral widths are similar. As a result, there is good overlap between the LED spectrum and the PPIX excitation spectrum.

An analysis of the relative effectiveness of different LED spectra and their overlap with the PPIX spectrum is shown in Figure 4. The Even's LED which has a peak wavelength of 635nm and a FWHM of 21nm has effectiveness (by definition) of 1. The Cevira CL7 Device is likely to have LEDs with a peak wavelength of ~635nm and a FWHM of around 15-16nm due to the fact that the LEDs are used at relatively low power levels. As a result, the effectiveness of the Cevira CL7 Device light source will also be at least 1 (i.e. at least equivalent to the Even's LED).

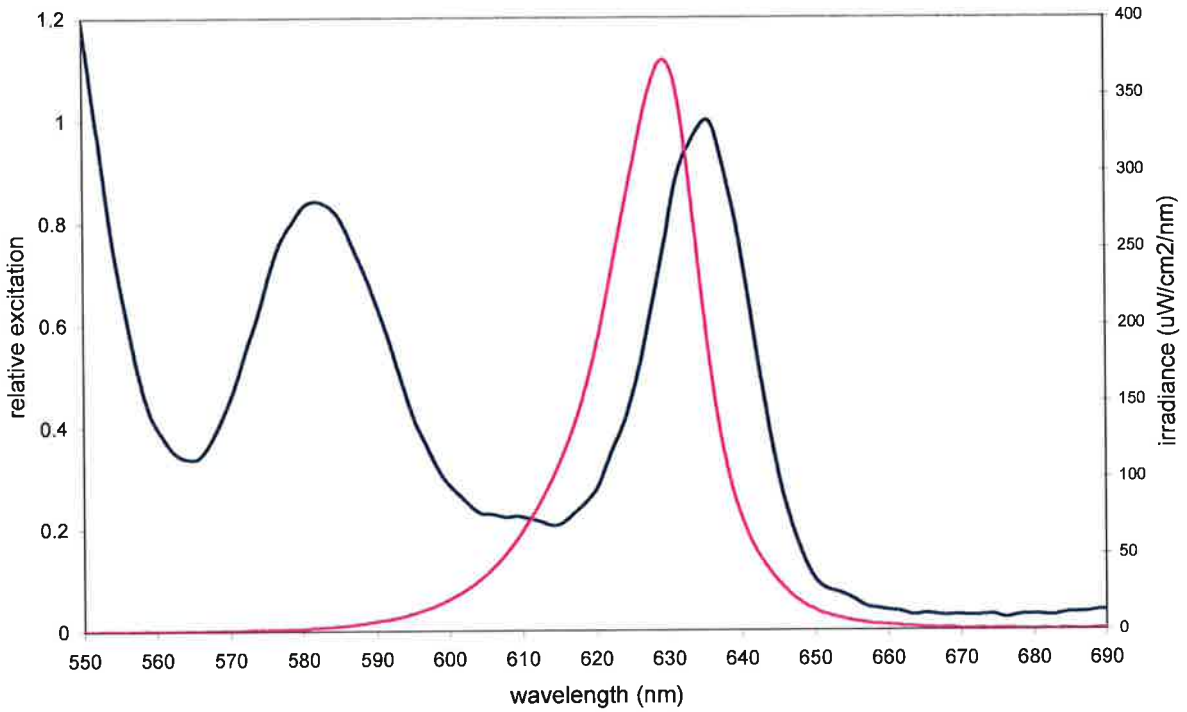


Figure 3: PPIX excitation spectrum and Cevira CL7 Device LED spectrum.

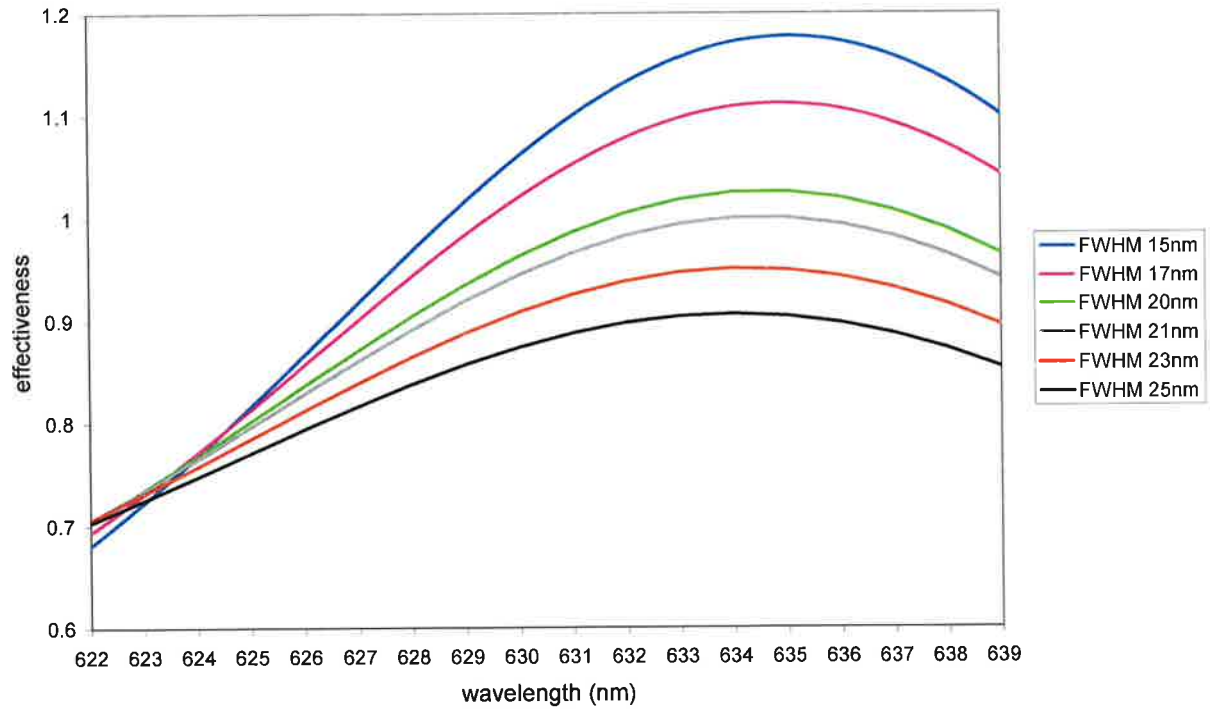


Figure 4: Effectiveness of different LED spectra in exciting the PPIX spectrum.

3.5 Battery

The Cevira CL7 Device will use a CR2 Photo Lithium Manganese Dioxide primary cell as the energy source.

During normal usage, it is currently estimated that ~6000J will be required from the battery in order to deliver the minimum dose (treatment time of 4.6 hours) discussed in the previous section.

This type of battery cell has been shown through testing to be capable of delivering up to 9000J at discharge currents between 100 -200mA. Examples of the measured discharge characteristics of two different types of CR2 Photo lithium cell (Panasonic and Power One) are shown in Figure 5. These tests were performed using a resistive load of 23Ω which gives a discharge current of ~120mA. This is similar to the levels which will be used in the Cevira CL7 Device.

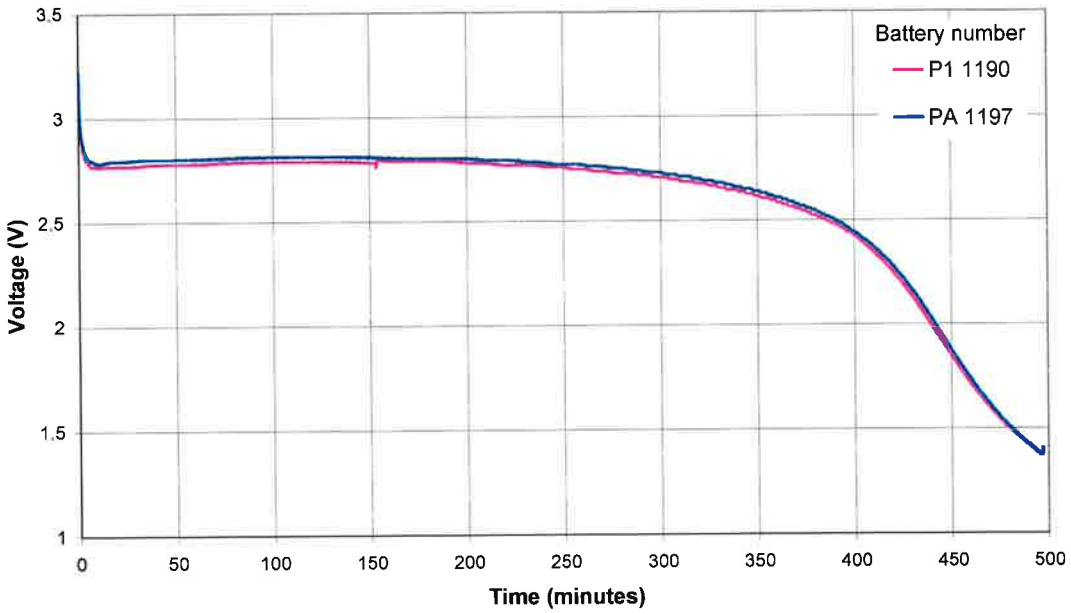
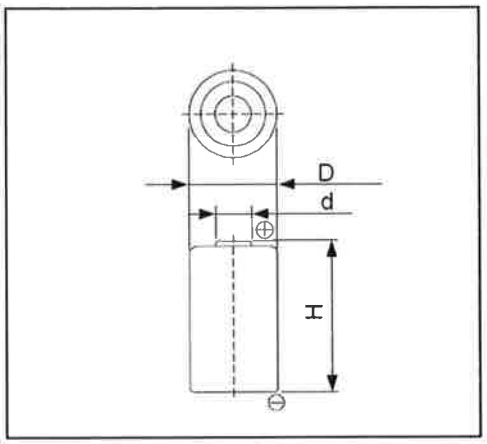


Figure 5: Discharge characteristics of CR2 photo lithium cell (Panasonic)

It is proposed that the Cevira CL7 device will be disabled when the battery voltage drops below 2.5V. From the results shown in Figure 5 it can be seen that over the range of discharge currents considered, the battery has the capacity to deliver over 7000J by this point.

A number of manufacturers produce suitable CR2 photo lithium cells e.g. Panasonic, Sanyo, Eveready etc.

Typical characteristics of this type of battery (Sanyo CR2) are given below:



Nominal Capacity*1		850mAh
Nominal Voltage		3V
Standard Discharge Current		10mA
Max. Discharge Current	Continuous*2	1000mA
	Pulse*3	2500mA
Temperature Range		-20°C～60°C
Weight		11g
Dimensions	D	15.6mm
	H	27.0mm
	d	6.3mm

*1 Nominal capacity is determined to an end voltage of 2.0V when the battery is allowed to discharge at a standard current level at 23°C.

*2 Current value is determined to be the level at which 50% of the nominal capacity is obtained with an end voltage of 2.0V at 23 °C.

*3 Current value for obtaining 1.0V cell voltage when pulse is applied for 15seconds at 50% discharge depth at 23 °C.

Typical Characteristics

The battery will be mounted in a battery holder in the Cevira CL7 Device with spring clips to ensure good electrical contact.

The battery will require certification according to UL 1642 or IEC 60086-4.

3.6 Activation

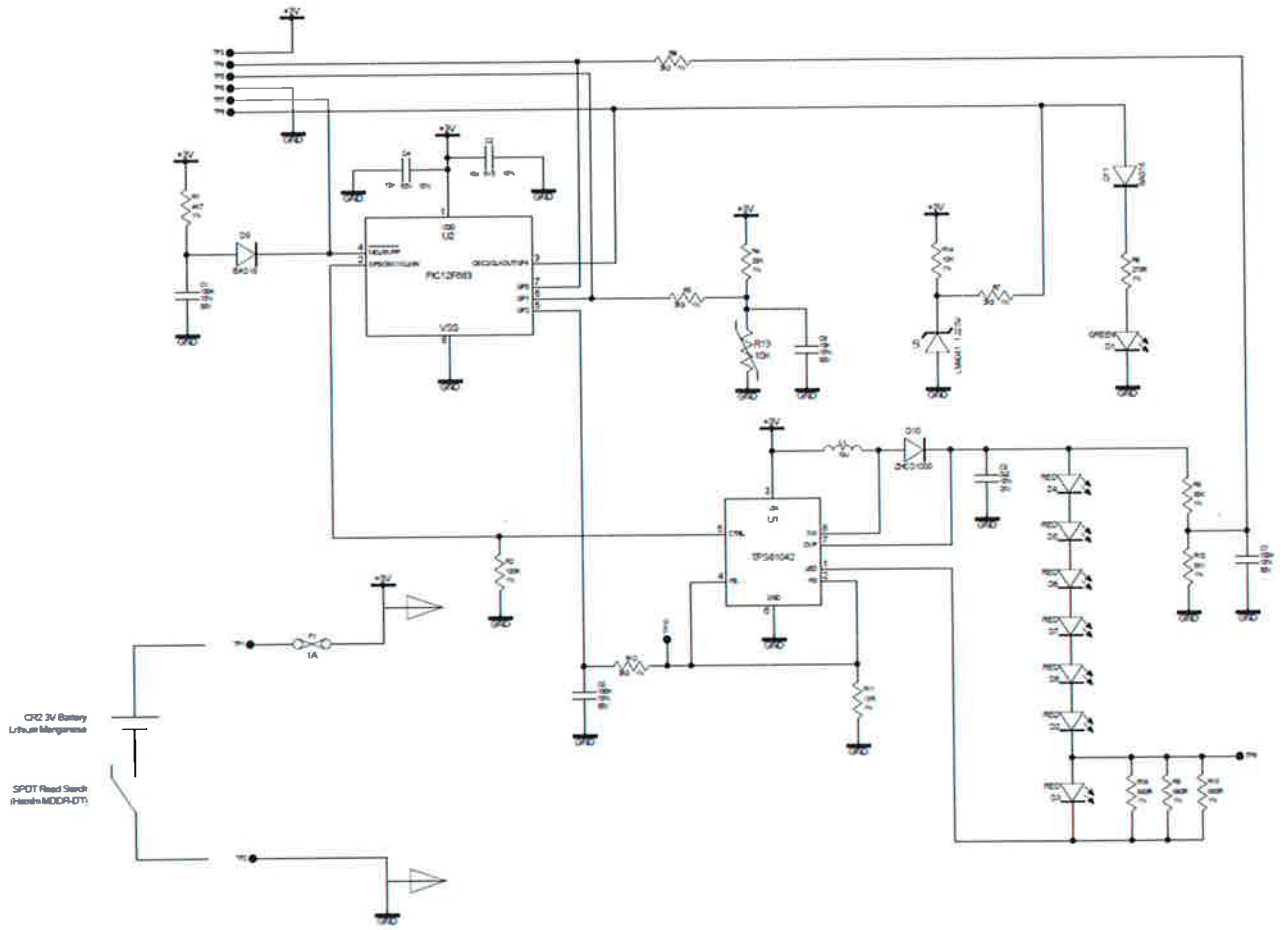
The Cevira CL7 Device will be activated using a reed switch in series with the battery. The switch will be set to be open immediately after manufacture by placing a magnet in close proximity to the reed switch. By holding this switch open until the device is used, no current will be drawn from the battery during shipping and storage.

The reed switch will be a normally closed type device (also referred to as a changeover type). An example of such a switch is the MDRR-DT miniature changeover switch manufactured by Hamlin.

4 Electronics Architecture

4.1 Circuit Configuration

The circuit configuration for the electronics is shown below:



The principal component groups in this circuit are:

- The seven red treatment LEDs (configured as a serial chain)
- The LED driver circuit (step-up DC-DC converter)
- The microcontroller

The microcontroller provides a platform to run the system software and provides the hardware 'glue' for the various control/monitoring functions. In particular, the microcontroller provides the following core functions and characteristics:

- 2048-word Flash (to provide program memory)
- 256-byte EEPROM (to provide non-volatile parameter memory)
- 128-byte SRAM (to provide volatile memory)

- Analogue input channels (10-bit A/D) for:
  - Measurement of LED current
  - Measurement of LED chain voltage
  - Measurement of battery voltage
  - Measurement of PCB board temperature
- General purpose digital output for:
  - Drive enable for LED driver chip
  - Green status LED
  - Serial diagnostic output (for debug purposes)
- General purpose digital input for:
  - Board test mode select
- Programming/test interface (test pads) providing
  - Access to chip in-circuit serial programming interface (clock, data, programming voltage)
  - Access to serial diagnostic output (for development purposes)
  - Means to place board into PCB test mode
- Operates down to supply voltage of 2.5V or less

The analogue input channels allow the system software to monitor the health/status of the device during periodic health-checks to ensure that critical parameters stay within expected limits and that the therapy is being correctly delivered. From a safety perspective they can be considered as 'protective measures'. The battery voltage is determined by measuring an external voltage reference because the microcontroller's internal analogue-to-digital converter is scaled/referenced to the (battery) supply voltage

It should be noted that in the design a number of the functions are shared on the same processor pin (e.g. battery/Vref measurement, green status LED and serial diagnostic output on pin 3)

4.2 Critical components

4.2.1 LEDs

Luxeon Rebel LEDs

In order to deliver light at the required wavelength and intensity to produce effective treatment within the specified timescale 7 Red high intensity Luxeon Rebel LEDs are used.

The 7 Red Rebel devices are driven in series using a current drive source. The nominal drive current is fixed at ~20mA.

The central LED is fitted with a shunt resistor which reduces its current to ~10mA. This enables the irradiance distribution in the Cevira CL7 Device to be made more uniform near the apex and helps reduce the temperature at the surface of the cap.

In this application the Rebel LEDs are operated at significantly lower drive currents (20mA) than their nominal ratings (typically 350mA).

LED Selection and Binning

For a full description of Luxeon LED binning, see Luxeon Technical Datasheet DS56.

The part number for the Red Rebel LED which are used is:

- LXM2-PD01-0050

The LEDs are binned by the manufacturer according to a number of parameters:

- Luminous intensity
- Wavelength
- Forward voltage

Lumileds specify the binning of their Rebel LED products using a 3 digit alphanumeric CAT code which follows the following format:

ABC

where A = flux bin, B = colour bin and C = forward voltage bin. The parameters are specified at a nominal drive current of 350mA and a device junction temperature of 25ºC.

It has been established that the following binnings are most appropriate for this application.

- **A flux bin**

A = H

The H bin refers to the Photometric luminous flux and is within the following limits:

>50 lumens, <60 lumens

Higher flux bin devices could also be considered for this application and may be desirable if they give and improved lumens/Watt efficiency. However, it should be noted that the LEDs in each device should be taken from the same luminous flux bin.

- **B colour bin**

B = 4

This colour bin determines the dominant wavelength and for bin #2 this is as follows:
Dominant wavelength > 620nm, <630nm

- **C forward voltage bin**

C = W

The W bin refers to the forward voltage and is within the following limits:

W bin: >2.00V, <2.20V

The bin which has therefore been identified a suitable for use in the Cevira CL7 Device product is:

H4W

It should be noted that since the LED drive currents used in the Cevira CL7 Device (~20mA) will be significantly lower than the nominal values used by Lumileds when specifying the LED characteristics (350mA), the actual values obtained will differ from the values specified.

4.2.2 Microcontroller

The selected microcontroller is the Microchip PIC12F683 and the following table defines the mapping of the functional requirements onto the microcontroller pins and peripherals

Function	Pin	Microcontroller Function	Capability / Comment
Power supply	Pin 1 (VDD) Pin 8 (VSS)		
On-chip Flash	n/a	FLASH	
On-chip EEPROM	n/a	EEPROM	
Programming interface (Vpp)	Pin 4 (MCLR/VPP)	ICSP	Also acts as external reset
Green status LED	Pin 3 (GP4/AN3/CLKOUT)	GPIO Port	
Serial diagnostic output		GPIO Port	For development purposes
V_{ref} analogue input		A/D	Used to determine battery voltage
LED driver enable	Pin 2 (GP5)	GPIO Port	
LED current sense	Pin 5 (AN2)	A/D	
PCB board temp sense	Pin 6 (AN1/GP1/ICSPCLK)	A/D	
Programming interface (clock)		ICSP	
LED voltage sense	Pin 7 (AN0/GP0/ICSPDAT)	A/D	
Programming interface (data)		ICSP	

4.2.3 LED driver

The LED driver chip acts as a step-up DC/DC converter (in combination with an external inductor) to generate a high voltage supply rail for the LED chain from a low-voltage (< 3V) battery supply. Converter chips suitable for driving LED chains are available from a number of manufacturers. In this application the converter chip ideally needs to have the following characteristics:

Characteristic	Preferred Target	Comment
Input supply voltage	≥ 2.5V	To deal with battery droop during treatment
Efficiency	≥ 80% (supply voltage ≥ 2.5V)	To minimise treatment duration and excess thermal dissipation
Regulation	Constant current output over desired input voltage range	To produce fixed LED current/irradiance during course of treatment regardless of battery voltage

Size	Minimal additional external components (excluding inductor)	To minimise PCB footprint of complete converter solution
Max storage temp	≥ 125°C	To facilitate over-moulding at 120°C (note this requirement is no longer applicable to the Phase 3 device)

The following table lists the chips that have been considered and ranks their key characteristics against the target values (green tick = meets target, orange question mark = marginal, red cross = does not meet target):

	Zetex ZXSC310		**Nat Semi LM3500**		**Linear Tech LT1932**		**Texas TPS61042**	
Min supply voltage	**0.8V**	✓	**2.7V**	✗	**1V**	✓	**1.8V**	✓
Efficiency	80-84% (measured)	✓	~ 80% (datasheet)	✓	~ 70% at 2.5V (measured)	✗	78% at 2.4V (datasheet)	✓
Regulation	Poor. Output current varies linearly with supply voltage	✗	Good. Includes constant current source	✓	Good. Includes constant current source	✓	Good. Includes constant current source	✓
Size	Medium. Needs external transistor and schottky diode	?	Small. Does not need external transistor or diode.	✓	Medium. Needs external schottky diode.	?	Small (DFN-8). Needs external schottky diode.	✓
Max storage temp	125°C	✓	Not quoted. Max operating junction temp is 150°C.	?	150°C	✓	150°C	✓

It can be seen that the TPS61042 fits all the requirements. On this basis the driver chip chosen for the Cevira CL7 Device trial units is the Texas TPS61042.

4.2.4 Temperature rating

The following table lists the rated storage temperature for the proposed critical components, all of which are compatible with the proposed production process.

Part	**Manufacturer**	**Description**	**Max storage temp**
ZHCS1000	Zetex	Schottky Diode (SuperBAT)	150°C
LXM2-PD01-0050	Philips	RED High Power LED (REBEL 50lm)	135°C
744042100	Wurth	10u Power Inductor (WE-TPC)	125°C max operating temp (no storage temp quoted)
TPS61042	Texas	TPS61042 LED Driver	150°C

PIC12F683-1/SN	Microchip	PIC12F683 8-Bit Microcontroller (SOIC)	150°C

Other non-critical components (e.g. resistors, capacitors etc) have been selected in the same way as part of the design process.

4.3 Single Point Failure Analysis

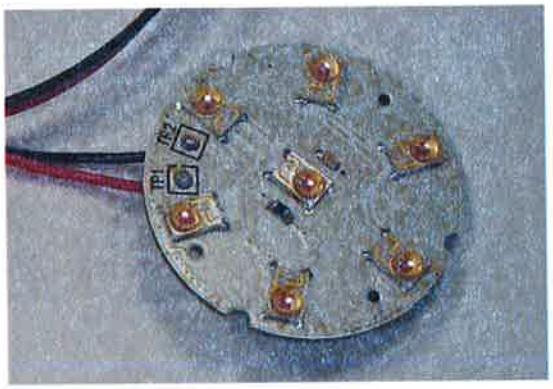
A single-point failure analysis has been conducted on the proposed circuit configuration to identify any aspects critical to device safety including short-circuit (SC) and open-circuit (OC) failures:

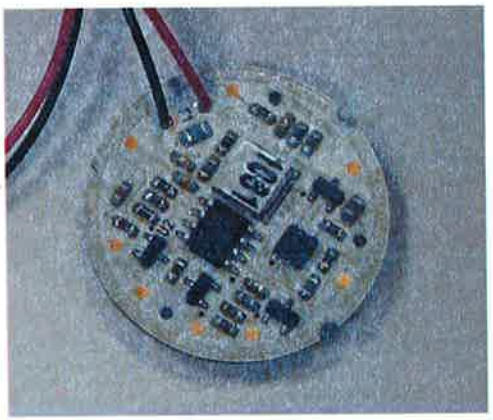
Failure Mode	Effect	Severity (high/med/low)	Proposed mitigating action
Battery – internal SC	Battery heats up/vents	High	Use UL-approved battery. Obtain failure statistics from manufacturer if possible. Test battery during production to look for anomalies.
Battery – external SC	Draws excessive current from battery - battery heats up/vents	High	Provide over-current protective measure (fuse)
Decoupling cap SC	Draws excessive current from battery - battery heats up/vents	High	Provide over-current protective measure (fuse)
Treatment LED SC	Partial illumination loss - reduction in delivered dose	Low (effects efficacy, not safety)	Monitor voltage across LEDs as part of periodic health-check (i.e. protective measure)
Treatment LED OC	No LED current - no dose delivered	Low (effects efficacy, not safety)	Monitor LED current as part of periodic health-check (i.e. protective measure)
Sense resistor SC	Larger LED current - increase in delivered dose	Medium	Monitor LED current as part of periodic health-check (i.e. protective measure)
Drive transistor SC	Draws excessive current from battery – battery heats up/vents	High	Provide over-current protective measure (fuse)
Drive transistor OC	No LED current – no dose delivered	Low (effects efficacy, not safety)	Monitor LED current as part of periodic health-check (i.e. protective measure)
Schottky diode SC	Change in LED current - change in delivered dose	Medium	Monitor LED current as part of periodic health-check (i.e. protective measure)
Schottky diode OC	No LED current – no dose delivered	Low (effects efficacy, not safety)	Monitor LED current as part of periodic health-check (i.e. protective measure)

Thermistor SC/OC	Wrong temperature measurement – loss of protective measure or treatment aborted early	Low (effects efficacy, not safety when considering single point failures)	Monitor thermistor impedance (i.e. temperature) and check it stays within expected range
Voltage ref SC/OC	Wrong current, voltage and temperature measurements – loss of protective measure or treatment aborted early	Low (effects efficacy, not safety when considering single point failures)	Monitor battery voltage, LED current, LED voltage and temperature and check they stay within expected range

4.4 Construction

A single rigid PCB holds the seven treatment LEDs on one side, and the driver circuit on the reverse side (see photos)





The PCB has the following constructional characteristics:

- Fully rigid construction (FR4)
  - Note: a flexi-rigid construction was used on the functional demonstrator but this is considered to expose the outer LEDs to damage from the increased lateral flexing action within the silicone moulding. A fully rigid construction is used to improve the resistance of the device to damage at the expense of slightly impaired mechanical flexing.
- Facility for connection of battery harness, via wires soldered direct to the PCB
- White solder resist and/or silk screen on bare upper surfaces (to increase light scattering)
- Test pads to allow external connection to the programming/test interface during production
- Mechanical features to hold the assembly in the tool during over-moulding
  - Location holes to provide accurate rotation in the tool
  - Mouse holes around the perimeter of the PCB to provide accurate 'levelling' within the tool

4.5 Power Consumption

The worst-case quiescent and typical active current consumptions for the constituent parts of the Cevira CL7 Device electronics are as shown below:

	Quiescent Current (worst-case)	Typical Active Current
LED chain (260mW dissipation)	0 mA	108 mA (note 1)
LED driver	~ 0 mA	~ 3 mA
Microcontroller	0.7mA (note 2)	0.7mA
Green indicator LED	0 mA	7 mA
Passives	< 0.5 mA	< 0.5mA

Notes:

1 Assumes 260mW dissipated in LEDs with 20mA LED current at 80% conversion efficiency
2 Assumes microcontroller not placed into power-down mode at any time

The resulting total power consumption of the Cevira CL7 device in both idle (i.e. pre-treatment and post-treatment) and active (i.e. treatment) states is shown in the following table. This is based on the pattern of LED flashes defined in section 2 for the various pre-treatment, treatment and post-treatment states.

	Active	Idle		
	Treatment	Pre-treatment	Post-treatment (success)	Post-treatment (error)
Current consumption (260mW LED dissipation)	112 mA	2.2 mA	1.3 mA	4.3 mA
Total power consumption (260mW LED dissipation)	336 mW	6.6 mW	3.9 mW	12.9 mW
Hourly battery energy consumption (260mW LED dissipation)	1213 J	23.6 J	13.8 J	46.9 J

It can be therefore be inferred that a 5.25 hour wait/absorption (pre-treatment) period followed by a 4.6 hour treatment would require ~ 5700J (c.f. > 7000 J available).

In practice (based on measurements on a series of product prototypes) it is observed that the actual total power consumption with the treatment LEDs illuminated is of order 320 mW (c.f. 336mW in above table) which provides an additional useful margin.

5 Software Architecture

5.1 Development Environment

The Cevira CL7 Device system development environment falls into two main categories: target-specific (PIC) and PC. The PIC development tools are required to write the firmware that is loaded onto the device, whilst the PC software is required to support the target and engineering interface (see section 5.7.3 for more information).

5.1.1 Source Control

Source control will be used throughout the software development. Microsoft Visual SourceSafe (Vss) is used to control all source code and associated files.

5.1.2 PIC

MPLAB IDE (currently v8.40) is a fully-featured development environment for PIC devices, supports all the standard compiler and debugging tools (specifically the Microchip ICD 2) and connects directly to Vss.

The Hi-TECH PICC v9.70 ANSI C compiler is used within MPLAB. It offers a very mature set of features, including EEPROM read/write functions and offers full support for the target device.

5.1.3 Win32

During development, simple software test harnesses and basic engineering interface applications have been developed using Microsoft Visual Studio (2005 or later) which supports high-speed application prototyping. All Win32 development uses C++, in order to provide direct compatibility with the target code (written in C). Visual Studio also supports Vss directly.

5.2 System Context

The software system context illustrated in Figure 6 shows the resources to which the software must interface. The dotted boxes indicate internal microprocessor resources, whilst shared colours show which devices share a common interface. Where applicable, microprocessor pin identifiers are displayed.

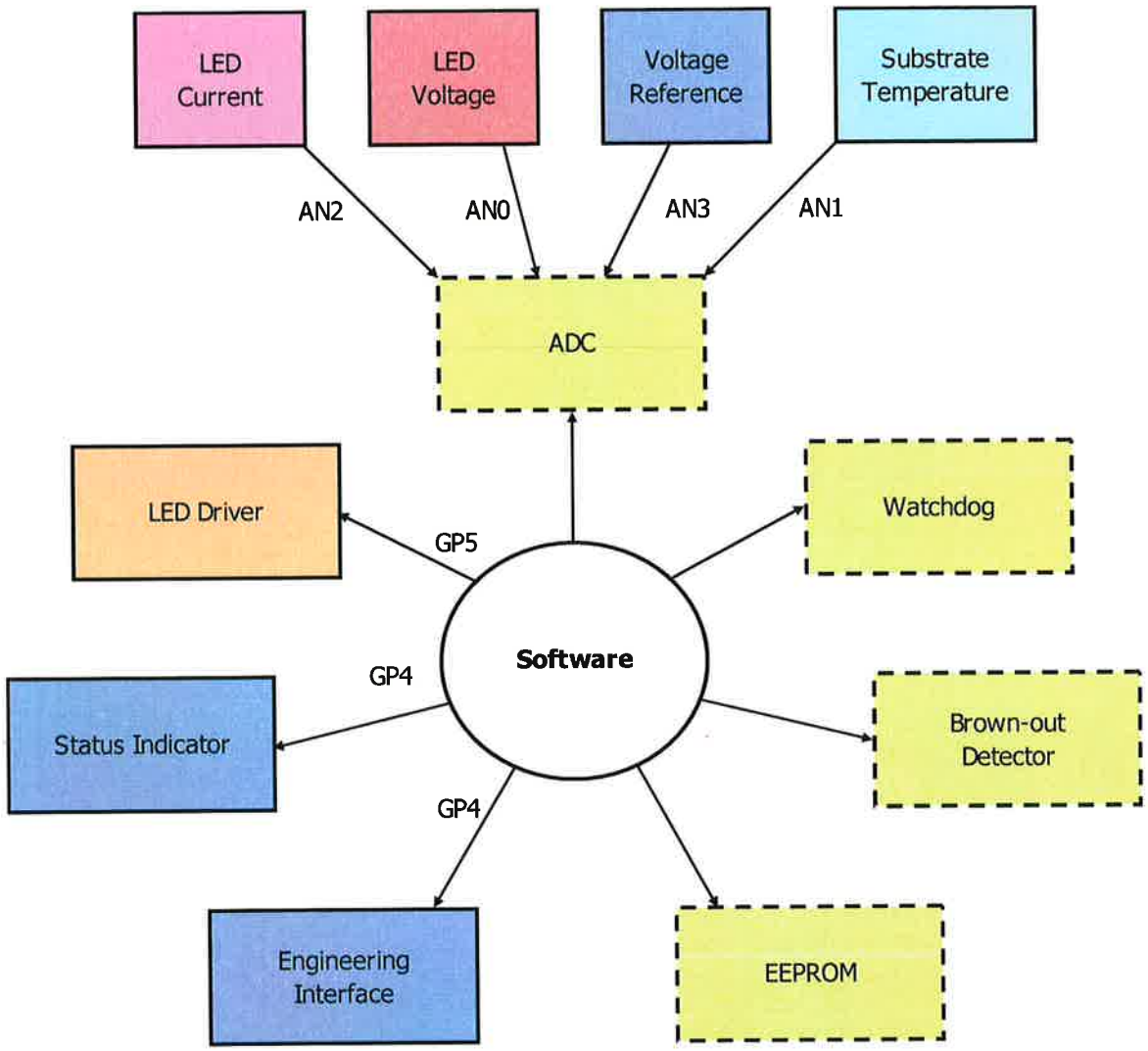


Figure 6 - Software System Context

5.3 Program Flow

There are three modes of operation for the system:

- Treat
- Board Test
- Device Test

At boot time, the mode of operation is determined as described in Figure 7, and the program proceeds as described in the use cases found in the SRS.

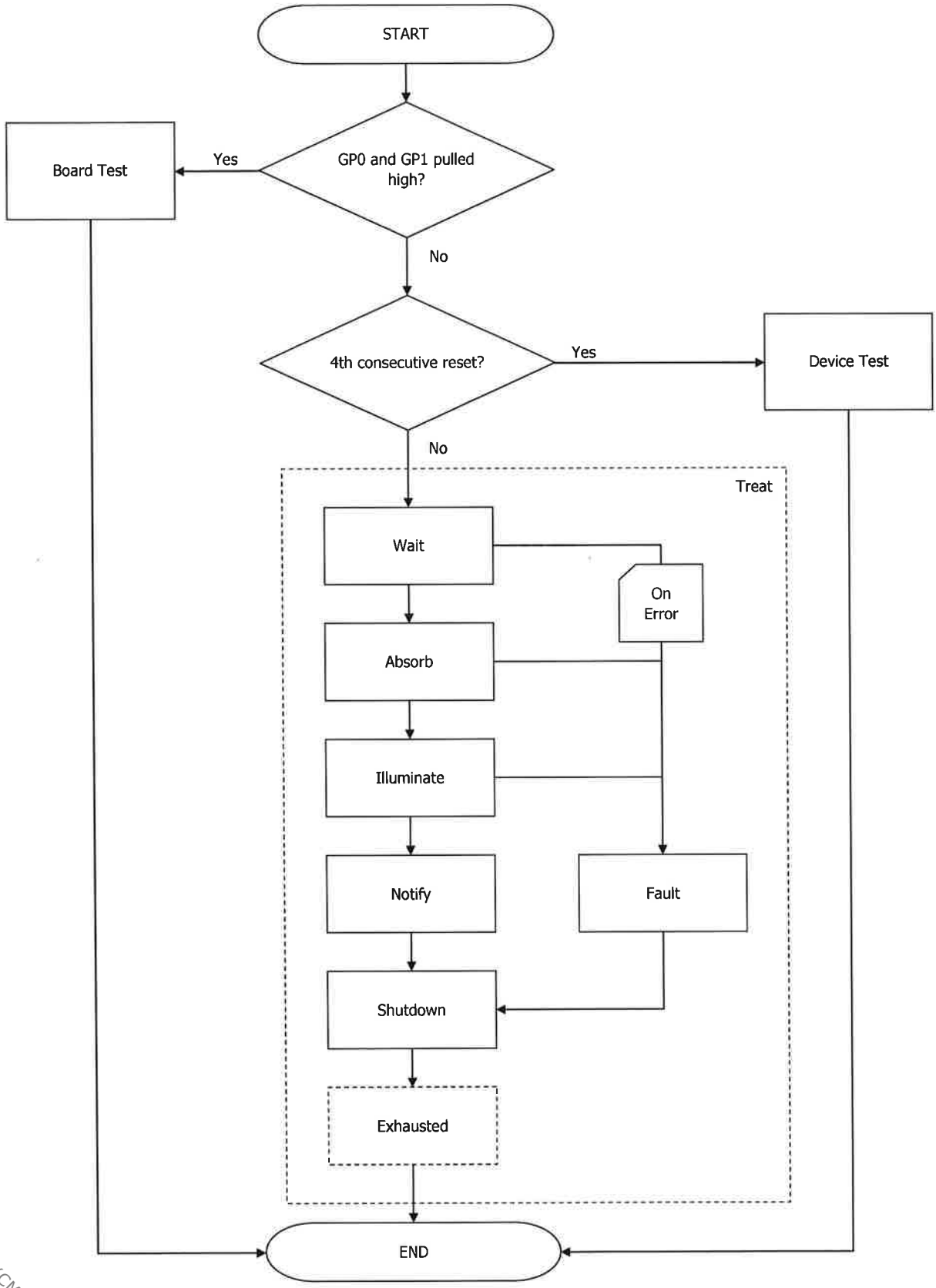


Figure 7 - Program Flow

5.4 Architecture

The context diagram shown in Figure 6, together with the program flow diagram (see Figure 7) and the use cases specified in the SRS, suggest the software architecture illustrated in Figure 8.

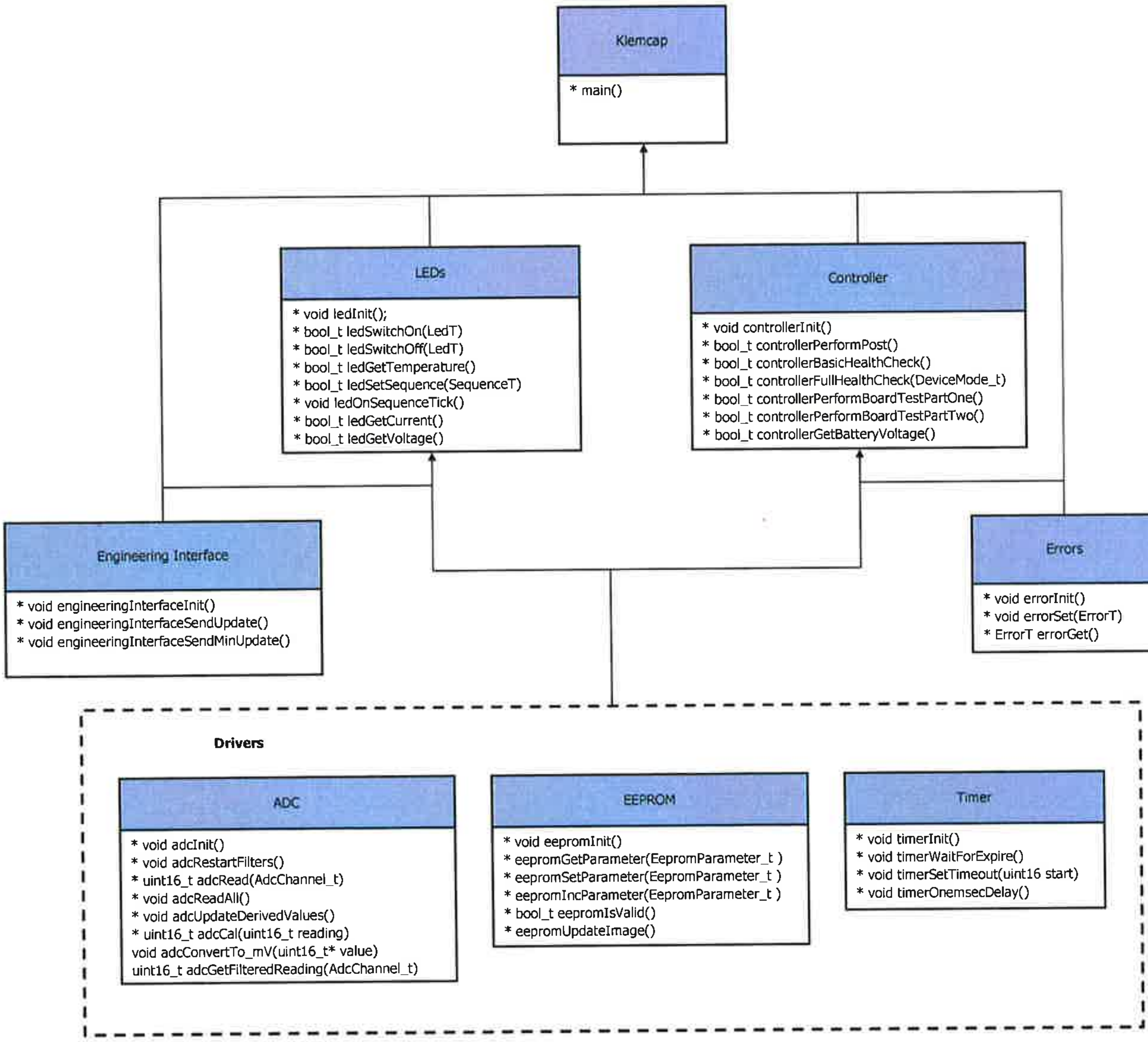


Figure 8 - Software Architecture

The program entrypoint in the Cevira CL7 Device module handles the program state machine (illustrated in Figure 7, described in the SRS), and performs all subsystem initialisation.

The LED module handles all LED-specific operations (for both the red treatment LEDs and the green status LED), including monitoring functions for temperature, voltage and current. The range of supported device temperatures is such that conversion of ADC values into the corresponding temperature is achieved using a simple 3-point interpolation. A set of functions are provided to support sequenced LED flashing with a simple timing interface that can be driven by the system timer module.

The error module offers an encapsulated interface for handling system errors.

The controller subsystem supports compound operations including device POST and system health checks.

The engineering interface is shared with the green status LED. Serial I/O is available only when the LED module is not driving the green status LED.

The EEPROM driver offers a set of accessors that abstract away from the byte-wise storage interface and deal with "real" data structures (see section 5.6).

The system timer driver implements a variable-delay polling interface with a granularity between 8µs and 500ms.

5.5 Threading Model

The threading model required by this system is easily determined from a simple timing analysis, shown in Table 2.

Action	Max Duration	Min / Max Interval
Flash[1] LED(s)	N/A	10s / 20s
Health Check	N/A	10s
Engineering Interface Update	80ms	>= 1s
EEPROM erase/write	6ms	N/A
A/D Conversion	1ms	N/A
Update Health Data Log	<~100ms	2s / 15mins

Table 2 - Software Timing Analysis

It is clear that everything can be driven from the main loop (i.e. no interrupts are required) because there are so few coarsely-timed operations to perform during program execution. EEPROM access and engineering interface updates cause the longest blocking delays in the system. At less than 100ms duration for each in the worst-case, all system calls can block, removing the need for thread synchronisation. Note however that 'block' EEPROM accesses must be limited to <16 bytes (EEPROM writes can require up to 6ms each).

During initialisation there are several special cases where functions are allowed to hold up execution (e.g. on entry to Board Test mode, processing is held up until all GPIO pins are released by the test jig). These special case do not impact the decision to implement an interrupt-free system.

Timer1 is 16-bit and operates with a 1/8 prescaler, generating ticks at 125 KHz. A count to approximately 12500 at this rate generates a 100ms delay, which is used to accurately time program execution.

5.6 Non-volatile Parameters

As described in the SRS, the system is required to store a number of non-volatile parameters. The PIC implements a byte-addressable memory space (256 bytes total), which is accessed by low-level read/write functions in the EEPROM module.

[1] Note that all flashes are of duration N*100ms and therefore the LED driver is called every 100msec to update the "display".

The parameters listed in Table 3 are stored in EEPROM.

Parameter	Description	Size (Bytes)
LED_OPERATING_TENSEC	16-bit record of the total time for which the CPU has run on battery power (10-second ticks)	2
HEARTBEAT_TENSEC	16-bit record of the elapsed treatment time (10-sec ticks)	2
BOOT_TENSEC	16-bit record of the number of 1-second ticks since the CPU booted.	2
BOOT_COUNT	The total number of times the CPU has booted.	2
POWER_CYCLE_COUNT	Used to track the number of times system power has been cycled to determine the mode of operation.	2
FLAGS	Parameter bits used to indicate: • Brown out • Treatment started • Operating state (4 bits) • Operating mode (2 bits) • Error code (1 byte)	2
CHECKSUM	Updated after any EEPROM data change, such that the sum of all stored bytes = 0.	2
TREATMENT_HISTORY	Buffer containing multi-channel measurements taken at 30 minute intervals during the treatment (up to 5 hours)	8 x 11 = 88
RECENT_HISTORY	Circular buffer containing the most recent multi-channel measurements	8x3 = 24
	Total Byte Count	**126**

Table 3 - Non-volatile Parameters

The EEPROM is split into two 128-byte 'banks' each checksummed to zero. When any parameter is updated, the data is sent first to Bank 0, then the checksum is 'balanced'; finally the same changes are copied to Bank 1. In this way there is always one bank with a valid checksum, even if power is lost during an EEPROM write, allowing the most recent system status to be correctly recovered from the 'valid' bank after any power interruption.

5.7 Development Considerations

This section is discusses a few simple features that will simplify and expedite development.

5.7.1 Engineering Override

During development some of the release features (e.g. a full-length ABSORB state – 5 hours) need to be bypassed. Inclusion / removal of specific features is controlled using a set of #defines in header file 'system.h.'

5.7.2 EEPROM Analysis Tool

When EEPROM images are uploaded from the target, they will be in a raw hexadecimal format that is not human-readable. A simple EEPROM analysis tool is implemented in Excel to interpret the raw values and display them clearly. This tool will be useful during both development and trials and may prove useful for field fault diagnosis.

5.7.3 Engineering Interface

During development, on-board measurements taken by the system ADC need to be recorded in real-time for post-processing. The system EEPROM is not big enough to hold such data, so a basic bit-bashed 4800bps serial port is implemented. A simple Windows application has been written to decode the information into a human-readable format and store it to file for analysis.

5.7.4 Initialisation of local variables

In order to minimise code space, local variables are not initialised at the start of each function. Instead the programmer must make sure in every case that a local variable is assigned a value before being used in another expression. This requires extra care but gives a significant decrease in total code space.

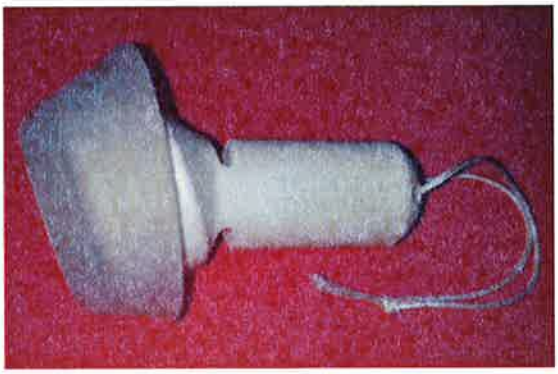
5.8 Manufacturing Considerations

PIC12F683s are shipped from Microchip with preconfigured internal oscillator configuration bytes loaded into special Flash locations. These locations are not changed by normal device programming.

6 Mechanical Architecture

6.1 Mechanical Form

The overall form of the assembled device is illustrated aside. The device is manufactured and supplied with the brim extended forward, but prior to fitting the brim is folded back as shown in the photograph to provide a surface that conforms to the vaginal wall.



The design illustrated above incorporates feedback obtained from initial form-and-fit studies.

6.2 Mechanical Construction

The following drawings define the overall form and construction of the Cevira CL7 Device.

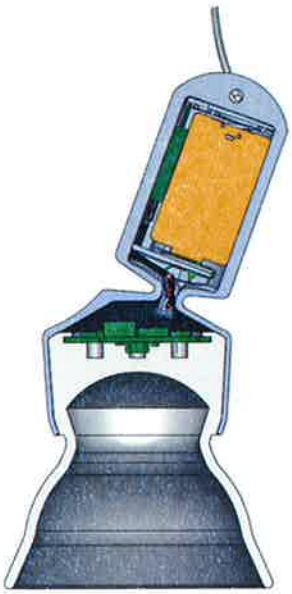


Figure 9: Cevira CL7 Device cross section showing key component parts.

Figure 10: 3 main components which form the Cevira CL7 Device shown in Figure 9. From left, transparent silicone lens with integrated brim, outer sleeve, electronics subassembly including battery, battery holder, PCB and wiring.

The device comprises three main mechanical parts:

- **Inner lens** – transparent silicone part with integrated brim which is folded back during insertion and use. The lens is designed so that the PCB can be inserted into it and retained during use with no need for gluing or over moulding.
  - tooled such that there are no split lines across lens surface
  - polished finish to the lens surface and LED cavities
- **Outer sleeve** – white pigmented silicone assembly which accommodates the inner lens and provides a housing for the battery holder, battery and associated reed switch.
  - tooled with split line running longitudinally along length of part
- **Electronic subassembly** – consists of battery, battery housing, reed switch, wiring harness and PCB

During manufacture, the PCB is inserted into the silicone lens, the battery is inserted into the outer sleeve and then the lens is inserted into the outer sleeve. The lens and outer sleeve are then glued using silicone RTV to form the finished sealed assembly.

The geometry of the inner lens is based on the mid-size Femcap® as this is a proven design that is designed to conform to the surface of the cervix. In this topology the treatment area extends across the concave inner surface of a cup which forms part of a larger spherical surface with the following characteristics:

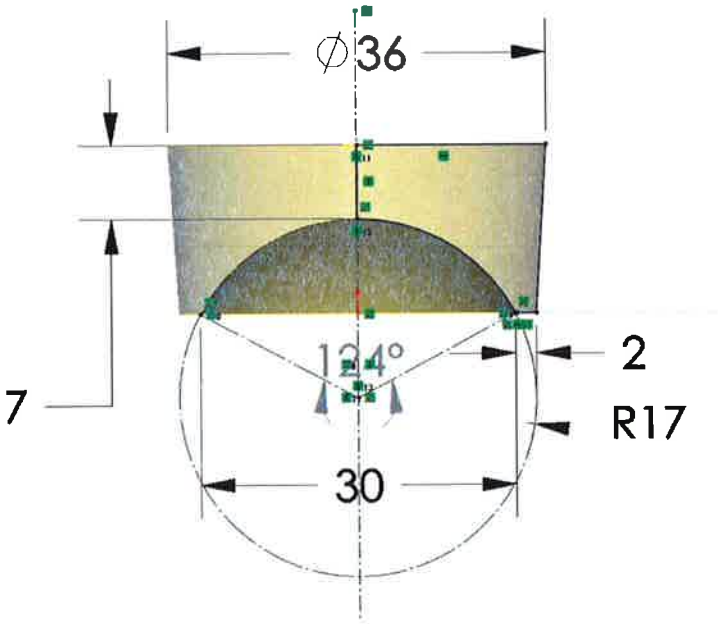
- Sphere radius of 17mm
- Physical cone angle of 124°
- Nominal cone angle for active treatment area of 100°

The dimensions of the resulting cup are:

- Cup diameter of 30mm at the rim (widest point)
- Cup depth of 9mm (rim to base at centre)

In practice, a tapered rim is added to the front circumference of the cup in order to aid with location to the cervix. The diameter at the top of the brim is 26mm (i.e. slightly less than the cup diameter)

The geometry of the cup component of the inner lens (excluding the outer tapered rim) is illustrated in the following diagram:



The active treatment area of the cup does not extend across the full cup surface and is considered to have a nominal cone angle of 100°

6.3 Materials Selection

The elastomeric materials used for the Cevira CL7 Device need to meet a number of specific requirements:

- **Optical properties** – the materials need to be available in both transparent (for inner lens) and bright white grades (for outer sleeve)
- **Biocompatibility** – the inner lens, outer sleeve and any associated bonding compounds will be in intimate contact with the surface of the body and need to be chemically/biologically inert and certified to ISO10993
- **Hardness** – the outer surface must have a soft feel while providing sufficient robustness to resist accidental damage during insertion and use. A silicone material with 30-50 shore hardness provides the right balance between device robustness and surface compliance.

The following materials have provisionally been selected for the Phase 3 trial units:

Usage	Material	Comment
Inner lens	Nusil MED-4940 Liquid Silicone Rubber	Typically 40 shore hardness Can be cured at high temperature in this application (150°C for 800 s) No post-curing required
Outer sleeve	Nusil MED-4940 Liquid Silicone Rubber	Typically 40 shore hardness Can be cured at high temperature in this application (150°C for 800 s) No post-curing required
	Nusil MED-4900-1 white pigment	4% mix ratio
Bonding	Nusil MED3-4013 Medical grade silicone adhesive (RTV)	
Pull Cord	Medical grade suture	Metric size 8 or greater.

Note: both the MED-4940 LSR compound and the MED-4900-1 white pigment are separately certified to ISO 10993. They are mixed at the point of manufacture but from a regulatory perspective it is understood that this will not affect the biocompatibility status of the finished device.

7 Manufacturing

7.1 Manufacturing Concept

The key manufacturing steps for fabrication of the Cevira CL7 Device Phase 3 trial units are:

- Electronics fabrication
- Moulding of silicone components
- Final assembly, test & pack

A sub-contract supply-chain and manufacturing model will be adopted for the trial units. This is expected to involve two key vendors:

- **Contract electronics manufacturer (CEM)** who can populate the PCBs
  - As a component supplier certification to ISO9001 is sufficient for this supplier
  - Bare boards and all electronics components to be procured by the CEM
  - Assembled PCBs to be tested by CEM and free-issued to the moulder
  - The selected supplier for the Phase 3 trial units is CIL Ltd, Andover, UK
- **Contract Manufacturing Organization (CMO)** who can fabricate the moulded lens, outer sleeve, assemble the finished device, test, label and pack ready for dispatch.
  - Since this supplier will provide final product certification to ISO13485 is needed.
  - The selected supplier for the Phase 3 trial units is Nolato AB, Torekov, Sweden

The following section defines the three key manufacturing steps in greater detail.

7.2 Electronics Fabrication

Process Step	Constituent Operations	Note
PCB assembly	Procure electronic component	CEM to procure all electronic components
	Procure PCB bare boards	CEM to procure
	Populate PCBs	CEM to undertake
PCB test	Enter board test mode by applying appropriate logic level to test select pin on PCB programming/test interface as PCB is powered-up. • Automatically execute self-test - check Vref within bounds - check LED current within bounds - check LED voltage within bounds - check PCB temp. within bounds • Manually check supply current within bounds - to check converter efficiency • Manually check clock output within bounds - to check processor clock speed • Measure LED irradiance and, peak wavelength and spectral FWHM and check within bounds - on central axis	Test of boards does NOT include any form of calibration. Performance is assessed as part of the board test and boards that fall outside pre-defined acceptance limits are rejected (i.e. select-on-test) Test completion status signalled on indicator and treatment LEDs. CEM to test PCBs and free-issue to the CMO
Battery test	Characterise & select battery - check battery no-load volts within bounds - check battery on-load voltage within bounds	Testing of batteries is performed by supplier to minimise performance spread and to identify potentially defective batteries
Electronics assembly	Assemble battery holder - battery holder, reed switch, negative battery terminal spring, positive battery terminal clip	Battery holder permits device to be qualified using standard CR2 batteries from multiple vendors and provides a smooth protective casing that facilitates insertion into outer sleeve
	Attach PCB to battery holder assembly using soldering operation	Joint to reed-switch protected with heatshrink sleeve

7.3 Moulding Process

Process Step	Constituent Operations	Note
Mould lens	Mould lens using transparent silicone - injection mould - material spec as per section 6.3	Use standard high temperature cure with injection mould press
		Automated removal of part from tool
Mould outer sleeve	Mould outer sleeve using pigmented white silicone - injection mould - material spec as per section 6.3	Use standard high temperature cure with injection mould press
		Automated removal of part from tool

7.4 Final Assembly

Process Step	Constituent Operations	Note
Assemble final device	Manually push-fit lens/battery assembly into outer sleeve	Plastic insulation strip removed from battery before insertion. External magnet attached over device tail when complete.
	Apply adhesive to lens outer body using semi-automatic gluing jig. Apply pressure to external outer sleeve surface to ensure uniform application of glue.	Using RTV as bonding compounds.
	Add medical grade suture for use as a pull string. To be tied on with a single overhand knot.	Medical grade non-absorbable suture of metric size 8 or more is used.
Test and pack device	Visually inspect device. Enter device test mode by removing/replacing magnet three times (each activation < 10s) • Automatically execute self-test - check EEPROM - check Vref within bounds - check LED current within bounds - check LED voltage within bounds - check PCB temp. within bounds Measure LED irradiance, peak wavelength and FWHM and check within bounds - on central axis	Test of devices does NOT include any form of calibration. Performance is assessed as part of the device test and devices that fall outside pre-defined acceptance limits are rejected (i.e. select-on-test)
	Insert into blister pack and seal	

	Enter device test mode by removing/replacing magnet three times (each activation < 10s) • Automatically execute self-test - check EEPROM - check Vref within bounds - check LED current within bounds - check LED voltage within bounds - check PCB temp. within bounds Measure LED irradiance, peak wavelength and FWHM and check within bounds - on central axis	Test of devices does NOT include any form of calibration. Performance is assessed as part of the device test and devices that fall outside pre-defined acceptance limits are rejected (i.e. select-on-test)

8 Regulatory Issues

8.1 Safety

8.1.1 Battery

In order to comply with IEC 60601-1 there are a number of requirements relating to the battery:

- The battery must be certified to UL1642 or IEC 60086-4 – most/all standard CR2 batteries will meet this requirement as supplied
- A protective device is needed to prevent excessive discharge current that ensures safety in the event of a single fault condition (i.e. failure of a component in the electronics). In addition discharge current in the single-fault condition must be limited to a value that does not cause the maximum permitted temperature on the applied part to be exceeded. The following protective devices measures are provided in the Cevira CL7 Device:
  - A fuse to prevent excessive discharge current. The fuse is the first 'down-stream' component from the battery/reed-switch and creepage/clearance distance between the battery poles up to the fuse must comply with IEC 60601-1
  - A LED current monitoring circuit (combined hardware/software) that ensures LED current remains within specified limits
- Any specific hazards associated with the battery are covered in the Risk management File

The following additional measures will be taken for the Cevira CL7 Device battery:

- Batteries from leading-brand reputable suppliers will be selected. Panasonic and Varta have currently been identified as possible suppliers. Panasonic batteries are used for the clinical trial build.
- Batteries will be sourced with a certificate of conformity including manufacturing batch numbers
- Batteries will be subjected to 100% test prior to assembly to confirm that the battery characteristics (open circuit voltage, initial on-load voltage) fall within expected bands

The Cevira CL7 Device battery is accommodated within a custom designed battery holder in order to facilitate easy assembly and to provide batteries from multiple vendors to be readily incorporated.

8.1.2 Surface temperature

In use temperatures of applied parts will be documented according to IEC 60601-1 Ed.3.1.It is not anticipated that the surface of the Device will exceed 43°C in use.

8.1.3 Biocompatibility

The external materials of the Cevira CL7 Device are required to conform to the biocompatibility requirements of the ISO 10993 series of standards. ISO 10993-1 defines the overall approach for evaluation and testing and suggests relevant tests based on a number of defined categories. Devices are classified according to the nature of the body contact and duration of body contact.

"KLEM _VR02_0011_01 Biocompatibility" describes the performed and proposed testing of the Cevira CL7 Device with respect to biocompatibility according to ISO 10993 and the FDA draft guideline Use of international standard ISO-10993 "Biological evaluation of medical devices part 1: Evaluation and testing – April 23, 2013.

The Cevira CL7 Device is considered to fall into the following category:

	Category	Sub-category	Comment
Nature of body contact	Surface contacting device	Mucosal membrane	
Duration of body contact	Limited exposure (A)	N/A	Devices whose single or multiple use or contact is likely to be up to 24h

Referring to the standard, the relevant tests for the Cevira CL7 Device are:

- Cytotoxicity (extracting in cell medium ± serum) (ISO 10993-5)
- Vaginal irritation (ISO 10993-10)
- Sensitization / potential for contact allergy (ISO 10993-10) In the US the guinea-pig maximization test (GPMT) is recommended over the local lymph node assay for "novel materials or when testing substances that do not penetrate the skin but are used in devices that contact deep tissues or breached surfaces" – Ref.: FDA draft guideline Use of international standard ISO-10993 "Biological evaluation of medical devices part 1: Evaluation and testing – April 23, 2013.

ISO 10993-5 and ISO10993-10 (Sensitization) test data are available for all the Nusil Silicone materials and adhesives used in the Cevira CL7 Device.

Vaginal irritation tests according to ISO10993-10 are planned during Clinical Phase 3.

A pull cord is attached to the sleeve to aid removal of the device after treatment. The Pull cord will be 510(k) cleared and biocompatible.

8.1.4 Indicators

IEC 60601-1 (3rd edition) imposes certain requirements on the colour of visual indicators. In particular it is a requirement that red indicators should only be used to provide a warning or an indication that immediate response by the operator is required. Consequently, it is not possible to use the red treatment LEDs alone to provide an indication that the treatment has completed successfully (i.e. by periodically flashing LEDs). The device design therefore includes an additional green LED that can be used for this purpose. In addition the red treatment LEDs are flashed prior to and during treatment to provide an indication that the LEDs are functioning correctly (see section 2).

8.2 Disposal

The European WEEE directive applies to medical devices in general unless the device can be considered to be "infected product" in which case the device is considered to be exempt. The Cevira CL7 Device is not being treated as infected product and is therefore subject to the WEEE directive. Accordingly, disposal instructions are include in the Instruction for Use (i.e. do not dispose of in household waste) and the standard European WEEE symbol is included on the device label (which is applied to the device package).

For use in the US, local regulations concerning disposal of electronic household waste should be observed.