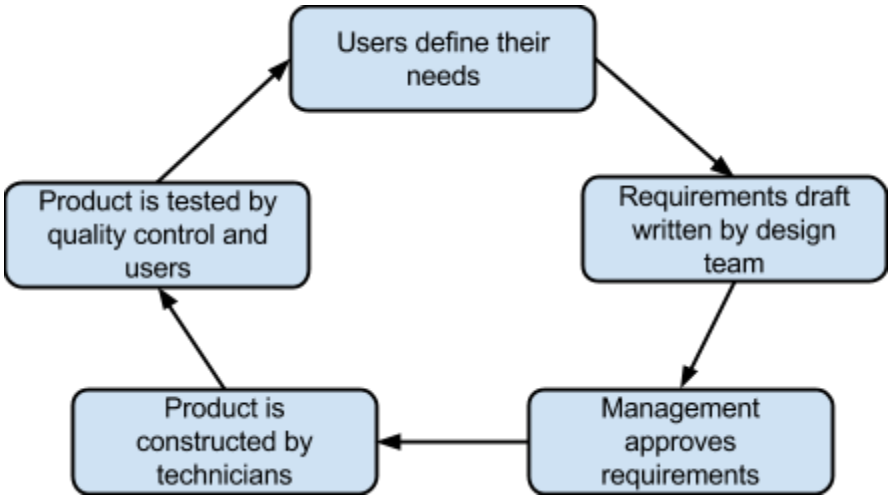
International Standards & the L.A.S.S.O.

Whilst designing and constructing the L.A.S.S.O. we read through current ISO documents that related to our device. The general form, ISO 9001, applies to all products whereas the medical form, ISO 13845, applies specifically to medical devices.

ISO 9001: 0.2 Process approach

We tried to adopt the quality management system into our design process through the general implementation of an organizational structure. This was based around: customers (CF patients and clinicians), technicians (Dundee iGEM 2014 team) and management (team supervisors). The iterative system focuses on *"improving the effectiveness of a quality management system, to enhance customer satisfaction"*. Below is a schematic of the procedures followed by organizations, that goes in line with quality management:



ISO 9001: 4 Quality management system

- **4.1 General requirements**

"The organization shall

a) determine the processes needed for the quality management system and their application throughout the organization,

b) determine the sequence and interaction of these processes,

…

f) implement actions necessary to achieve planned results and continual improvement of these processes"

In our case the customer would be the user with whom we had direct contact; the patients and clinicians at the Ninewells Hospital CF clinic. We started off by gathering the users requirements and amalgamating these requirements into a document. Our supervisors, the upper management in our structure, authorised the requirements document and we were able to construct the first L.A.S.S.O design. From this, we gathered more information from the users

with regards to their needs and considered changes that we should make to the device. This iterative process continued and we constructed another requirements document, which had to be approved before improving our L.A.S.S.O. design. Throughout our work on the L.A.S.S.O. we determined the sequence of our construction processes. We started off by working on basic circuitry and improving the photodetector's sensitivity. We then moved on to constructing a 3D printed case for our L.A.S.S.O. that would house the circuitry, along with the engineered *E.coli* from our biological system in a responsible and safe way.

ISO 9001: 5 Management responsibility

- **5.1 Management commitment**

"The management review shall include any decisions and actions related to…

a) *improvement of the effectiveness of the quality management system and its processes,*
b) *improvement of products related to customer requirements"*

In order for our supervisors to approve the design and construction of our device we constructed requirements documentation that went through their approval.

ISO 9001: 6 Resource management

- **6.2 Documentation requirements**

"A documented procedure shall be established to define the controls needed"

With regards to current documentation: we measured the results that we received from testing the device on controlled bioluminescent samples. We also documented all the equipment we used for constructing the L.A.S.S.O., along with all the components used in the design. The documentation of hardware and software used ensures that future iterations of the device could be made in the same way, thus achieving conformity.

- **6.4 Work environment**

"Determine and manage the work environment needed to achieve conformity to product requirements"

The processes that we followed had to be constructed by working in the appropriate environment. In our case, this included following the necessary lab procedures for constructing the biological system and safety protocols when working with the electrical circuit design.

ISO 9001: 7 Product realization

- **7:5:3 Identification and traceability**

"ensure that medical devices returned to the organization are identified and distinguished from conforming product"

To ensure traceability and identification in the future, we would establish a serial number system for each manufactured L.A.S.S.O. for ease of identification.

- **7:5:4 Customer property**

"The organization shall identify, verify, protect and safeguard customer property provided for use or incorporation into the product…(this) can include intellectual property or confidential health information"

The interface in the design will be able to store confidential health information of the CF patients. This would be included in a secure database.

- **7:6 Control of monitoring and measuring devices**

"a) where no such standards exists, the basis used for calibration and verification shall be recorded"

Due to time constraints, clinical sputum samples were not used to test the biological system. However, we created a prototype model, envisioning the future possibility of a coherent biological and electronic device. Furthermore since no calibrated scale exists for our biological systems and the bioluminescence they produce in the presence of bacteria, we would in the future record the calibration scale and document it.

"d) be safeguarded from adjustments that would invalidate the measurement result"

Within the L.A.S.S.O. the tests are run through a microcontroller,collecting the data at relevant points.This ensures that test measurements collected by the L.A.S.S.O. would not be invalidated. By placing a one way, filter-sterilizing valve into the sample plate, the future device would ensure that the biological system cannot be manipulated. This would ensure that patients are able to input their sputum and measure the bacterial load in it using the system without ever being able to modify the engineered *E. coli* directly, thus safeguarding the measurements made from being invalidated.

ISO 9001: 8 Measurement, analysis and improvement

- **8.1 General**

"The organization shall plan and implement the monitoring, measurement, analysis and improvement processes needed

a) to demonstrate conformity to product requirement"

In order to follow this standard we tested our prototype device several times. We carried out these tests using *Vibrio fischeri* concentration samples in order to prove that we could get consecutive results for the samples.

- **8.2.1 Customer satisfaction**

"...the organization shall monitor information relating to customer perception on as to whether the organization has met customer requirements"

We took our prototype back to the Ninewells Hospital CF clinic where we demonstrated the device to the users. Ethical approval was not sought for user testing as we showed the possible functionality of the L.A.S.S.O. without the users directly interacting with it.

- **8.3 Control of nonconforming product**

*""*if *deficiencies become apparent only after the product is in use, preventative action should be taken...to eliminate the causes of potential nonconformities in order to prevent their occurrence"*

After development and implementation into professional situations, ISO standards should ensure that the organization in charge maintains the quality management processes through monitoring. The procedure is to follow this through with customer satisfaction feedback once changes are made, creating a continual chain of feedback and improvement.

- **8.4 Analysis of data**

""The organization shall determine, collect and analyse appropriate data to demonstrate the suitability and effectiveness of the quality management system"

In order to do this we would also collect and analyse data that demonstrates how well the system works. This could focus on carrying our standardized re-runs of the working device. We

also planned to work out the errors within any repeats of our system. In the current prototype of the L.A.S.S.O. repeated data was collected, and the range within results was considered in order to ensure effectiveness of data.

- **8.5 Improvement**

““The organization shall continually improve the effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions and management review.”

There are many overlaps within ISO 9001 and ISO 13845, and most of the general requirements are taken directly into the medical device forms. We did however cover some aspects that appeared only in ISO 13845.

ISO 13845: 3 Terms and definitions

From ISO 13845 we found that the L.A.S.S.O. was categorized under the *“active medical device”* section which covered a *“medical device relying for its functioning on a source of electrical energy”*.

Although many of the specifications did not apply to our system, as they referred to implantable medical devices such as surgical equipment, we were able to follow general concepts.. This included the labelling on the L.A.S.S.O. and the instruction information which is included in the accompanying interface.

ISO 13845: 7 Design and development

- **7.3.6 Design and development validation**

“As part of design and development validation, the organization shall perform clinical evaluations and/or evaluation of performance of the medical device, as required by national or regional regulations”

Our device is simply a prototype and not one that can be used immediately in actuality. Before the L.A.S.S.O. could be used by CF clinicians or patients it would have to go through extended testing along with clinical trials. In order to adhere to ISO standards the feedback from these tests would be used to improve the device.