Development of Open source

Laboratory Information Management System

(LIMS)

For

Human Biobanking

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KEYWORDS

LIMS

Open-source

BioDrop μLITE

Qubit Fluorometric

Biospecimen

Bika

ABBREVIATIONS

LIMS	Laboratory Information Management System
AGL	Applied Genomics Laboratory
COTS	Commercial-off-the-Shelf
CSV	Comma Separated Values
DNA	Deoxyribonucleic Acid
FOSS	Free and 0pen Source Software
H3Africa	Human Heredity and Health in Africa
HIV	Human Immunodeficiency Virus
ID	Identification
MTBC	*Mycobacterium tuberculosis* Complex
OS	Operating System
RIF	Rifampin
RNA	Ribonucleic Acid
SA	South Africa
SOP	Standard Operating Procedure
SIGLa	Sistema Integrado de Gerência de Laboratórios
PC	Personal Computer
USB	Universal Serial Bus
ZMI	Zope Management Interface
TAL	Template Attribute Language

ABSTRACT

Biobanks are collections of biological samples and associated data for future use. The day to day activities in a biobank laboratory is underpinned by a laboratory information management system (LIMS). For example, the LIMS manages the execution of tests on biospecimens and track their movement and processing through the laboratory. There are a range of commercially available Biobank LIMS systems on the market but their costs are prohibitive in a resource limited setting. The cost of Commercial off-the-shelf software includes the initial cost of acquiring the system, as well as the cost of maintenance and support throughout the software's life cycle. The Bika LIMS system on the other hand is Free and open source software (FOSS) with decreased license cost, used routinely in non-medical laboratories.

Ideally, if Bika LIMS could be customised to handle human biospecimens, then both biobanks and genetics laboratories could benefit. Central to any biobank functionality in Bika LIMS is the ability to import information from routine biomedical equipment. We identified two instruments that are key to human biobanking and are lacking in Bika LIMS namely BioDrop μLITE and the Qubit Fluorometric instrument. Import interfaces for importing DNA/RNA concentration analyses from these instruments and management of the results with associated sample information would add value to the LIMS.

The aim of the thesis was to customise Bika LIMS for utility in a biomedical laboratory. In collaboration with colleagues at Tygerberg medical school, the Bika LIMS software was customised to accommodate the DNA and RNA concentration analyses results for a pathology laboratory and the LIMS workflows customised for use at Tygerberg medical school. In this process the manual operations of Tygerberg medical school laboratory would migrate to the use of Bika LIMS. The analytical module in Bika LIMS was implemented using PYTHON, by using logic that allows importing of specific analyses. A template was created for the BioDrop μLITE and Qubit Fluorometric instruments used for developing the interface for an analysis import form. The instruments generate results in CSV file format. A parser was created to read and parse the files uploaded from the import form, by splitting them into parts, extracting the data, and populating key-value pairs. The controller manages the submission of the form by initialising the parser that imports the specific file into the LIMS where it is managed by the configured Bika LIMS workflow.

Bika LIMS has been customised for BioDrop μLITE and Qubit Fluorometric instrument for use in the biomedical laboratory to accommodate DNA and RNA analyses. The customised software was installed and tested as a demo site. Multiple concentration results from DNA/RNA instrument analyses were tested and was successfully imported and managed by the LIMS. Further customisation of the software continues as part of an international collaboration to bridge biobanking activities between Europe and Africa.

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DECLARATION

I declare that *Development of Open sourceLaboratory Information Management System (LIMS) For Human Biobanking* is my own work that it has not been submitted for any degree or examination in any other university, and all the sources I have used or quoted have been indicated and acknowledged by complete references.

Toluwaleke Ademuyiwa January 2018

Signed:

ACKNOWLEDGEMENTS

The work on this thesis has been very challenging yet interesting and exciting at times. I owe most of what I have been able to complete to the patience and support of my supervisor, Professor Alan Christoffels. It had been a great honour and privilege to work with someone who is so highly studied and experienced. I hold dear all that Professor Alan Christoffels had taught me in word and action.

The confidence, love and encouragement of my mother and brother are hugely appreciated. They have always helped me achieve more than I thought possible for myself. The persuasion and excellent advice from my wife was also one of the reasons why I did not give up. I am forever indebted to them.

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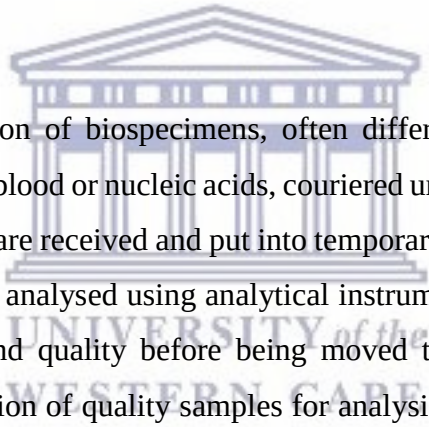
1 Rationale

Prior to the LIMS implementation, the Tygerberg pathology biobank used traditional approaches for data management. Their database consisted of a variety of files, such as multiple Excel spreadsheets, comma-separated values (CSV) and text files. The paper based record keeping method made updating and tracking of records complex, thus making data management a tedious and time consuming task. This thesis describes a laboratory information management system (LIMS) customised for biobanking to facilitate management of sample preparation in the biomedical laboratory. LIMS functionality encompasses the management of data generated in the laboratory and different features that support day to day operations in the biobank laboratory. The software tool supports the rapid implementation of detailed and adaptable workflows, with inherent underlying flexibility in its architecture to support diverse data tracking needs (Sciences, 2016).



Procedures used for preparation of biospecimens, often differ across laboratories. Human samples are received as whole blood or nucleic acids, couriered under various shipping controls and conditions. Biospecimens are received and put into temporary storage from where they are taken to be separated and then analysed using analytical instruments to determine the nucleic acid sample concentrations and quality before being moved to long term storage. Hence, efficient and accurate preparation of quality samples for analysis and management of all data about patients, biospecimens and tests results generated in the laboratory setting requires quality management and elimination of human error.

LIMS is the perfect way of managing this type of complex laboratory workflow and logistics. There are various commercial LIMS available, but their costs are prohibitive in a resource limited setting. Major disruption can occur when an organisation recommends a LIMS software where the laboratory operations fit into the LIMS, rather than developing or acquiring a LIMS that will fit into the laboratory procedure. The alteration of the procedures can complicate the entire laboratory workflow. A range of open source LIMS were reviewed and include Bika LIMS, OBiBa, AGL-LIMS, OpenFreezer, Open-LIMS, OpenSpecimen, Screensaver, SIGLa and OpenELIS. These open source platforms are used for management of samples and associated

data in the laboratory. Bika LIMS was the chosen open source LIMS for customisation because its user community has steadily grown since the software release in 2000. The growth of user community will help build a community resource that can advance the field by contributions to code repository, open access to Bika LIMS issues tracking system and support for future customisation of the software. This will assist developers to learn and share knowledge through asking and answering questions, which include an active international software developer community. Bika LIMS employ modern technology like Python to add new features to the system, Plone and Zope as content management framework and provision of adequate security and workflow audit trail which is one of the requirements of a quality LIMS (Spikelemire et al., 2002). This LIMS is built on an open source platform where additional functionality is supported by the continued development by the community, to ensure standard quality software with a constant growth in modern features and enhancements. The user community of Bika LIMS include the South African Wine Laboratory Association (SAWL) for managing wine analyses, and chemical and microbiological analytical services in corporate and agricultural industry. However, Bika LIMS was customised in this thesis for utility in a biomedical research laboratory for management of human biospecimens. One of the major benefits of a LIMS has been the improvement of data quality (Tagger, 2011). The analytical modules in LIMS were designed for importing of analysis results from the instruments, according to specific file format and structure. Bika LIMS was uniquely customised to meet the need of a biomedical laboratory by supporting the LIMS with a laboratory's preferred instrumentation, and accommodation of data coming off the instruments and customised for sample preparation option by allowing allows automatic uploads from import interface and management of human sample for future use. It will go a long way to support analysis of data and samples from the pathology laboratory. Development of a LIMS from the basic is capital and work intensive, however customising a LIMS often involves addition of software modules to produce more functional and efficient software that will cater for the specific laboratory needs. The work in this thesis will ensure quick and reliable access to BioDrop μLITE and Qubit Fluorometer concentration results and management of sample information. It is envisaged that the utility of the biobank LIMS functionality will extend to other biomedical research laboratories where day-to-day management of biospecimens and lab data are essential.

1.1 Analytical instruments

An analytical instrument is a laboratory device that qualitatively and quantitatively analyse samples and provides information about the samples. Bika LIMS has no instrument import interface that support biomedical technology such as BioDrop μLITE and Qubit Fluorometer. BioDrop μLITE is a suitable instrument used for micro volume measurements (Figure 1A). It has an in-built sample port with no moving parts. The methods are pre-programmed for DNA, RNA, oligos and proteins in the on-board software decreasing the time from measurement to results. Moreover, data generated using the on-board software can be stored internally or conveyed using a USB memory stick, or both the PC-only and standalone instruments can be controlled using a PC and BioDrop Resolution Software.

Qubit Fluorometer is a powerful, dual-core processor, user friendly instrument with touch screen that allows for easy workflow navigation (Figure 1B). The Qubit Fluorometer is a benchtop fluorometer analytical instrument that accurately measures DNA, RNA, and protein using the highly sensitive Qubit quantitation assays. The user access "fluorometer mode" by entering the sample name (Figure 1C). Calculations of the concentration of the samples are automatically performed by the instrument by choosing the applicable nucleic acid. Qubit Fluorometer technology gives a more accurate reading of DNA or RNA concentration, but cannot be used to pick up contamination in the sample. The fluorescent dye mix is added to each of the samples, as well as two standards provided with the kit and the resulting fluorescence is read by the Qubit. The sample values are then plotted against the standard curve to get the assay concentration, measured in ug/ml (Figure 1D). The user can save results and transfer data using the USB cable or USB drive (ThermoFisher, 2015).

BioDrop μLITE and Qubit Fluorometer instruments work a bit differently. Qubit Fluorometer instrument uses fluorescence to detect DNA and RNA. BioDrop μLITE determines the concentration and purity of DNA, RNA, oligos and protein. The major difference is that BioDrop μLITE shows a peak revealing the presence of contaminants. The results for samples containing DNA and RNA cannot be distinguished from one another, while Qubit accurately measures both DNA and RNA in the same sample. The instruments results data are exported and saved as CSV file.

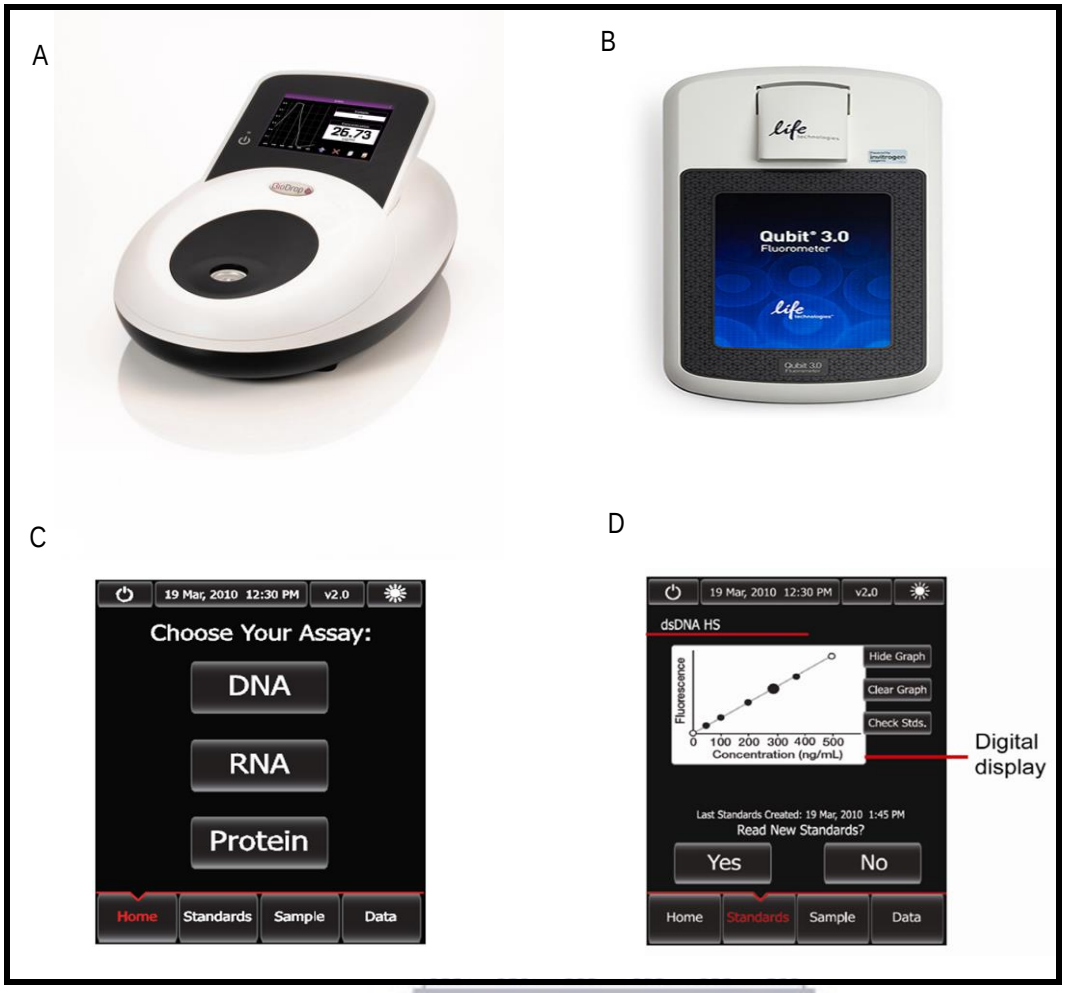


Figure 1: Instruments used for quantification of DNA and RNA. BioDropμLITE instrument (A) for micro-volume measurement, data acquisition and analysis. Preprogramed method for DNA, RNA, oligos and protein(source: BioDropμLITE). Qubit Fluorometer instrument (B) measures DNA, RNA and protein, and measures the concentration of DNA or RNA by using the highly sensitive fluorescence(source:ThermoFisher Scientific). Qubit® 3.0 Fluorometer (C) instrument screenshot showing how users access fluorometer mode. Qubit Fluorometer (D) prompting to choose between reading new standards and using the previous calibration.

1.2 Aims and objectives

The primary aim of this research is to create BioDrop μLITE and Qubit Fluorometer instrument import interfaces in Bika LIMS for importation of concentration results from DNA/RNA analytical data. Open source Bika LIMS was customised to specify preparation options used for sample preparation that are fundamental to biobanks but absent from the current non-DNA/RNA based laboratory functions. In collaboration with colleagues at Tygerberg medical school, the Bika LIMS software was customised to:

(a) Support BioDrop μLITE and Qubit Fluorometer instruments, so that concentration results from DNA/RNA analytical data are stored directly into the LIMS to eliminate transcription and typographical errors by creating an instrument import interface for the results generated.

(b) Accommodate and specify sample preparation workflow options used to manage a variety of human samples used in the laboratory.

(c) Provide a workable web-based alpha release of a LIMS for use by the Tygerberg Biobank laboratory.

2 Literature Review

A biobank is a biorepository that serves as storage for a large collection of human biological samples, and their associated information, amass for research and future use (Baker, 2012). These biospecimens and related data are used by scientists to ultimately gain insight into mechanisms of human diseases that will inform a health intervention strategy.

Prior to 1982 laboratory notebook and handwritten reports were used to track and report information (Bentley, 1999). Data tracking and data management software programs were developed to reduce the bottleneck of recording and tracking of data. The first elementary off-the-shelf LIMS was introduced in 1982. By 1990 to 1999, programming and documentation was made easier by personal computers and software databases. Most software system issues then were as a result of complex software installation, and need to ensure that the program works properly with the related systems (Bentley, 1999). Also, laboratory management software needs to integrate with equipment software installation. Workflow processes changed as technology advanced and the need for application specific function became paramount (Bentley, 1999). In the 21st century some LIMS had added additional features that redefined LIMS, which include the interfacing of instruments data with a laboratory system. Interface is a shared boundary where two or more independent systems exchange information, which can be between software and peripheral devices.

2.1 Biobanking in South Africa

The value of large scale genetic studies in South Africa (SA) is underscored by the increase use of DNA and RNA sequencing based technologies that provide a wealth of genomic data to unravel mechanism of disease progression. Collaborative biomedical research with access to large collections of samples and data provides a catalyst for the development of early diagnosis and drug discovery (Abayomi et al., 2013). This dramatic increase in the collection of biological samples and their associated data has led to development of vast amounts of biobanks in SA and across the African continent. However, this development could pose a great challenge to the developing world unless there is a commitment to revolutionise the systems that manage critical responsibilities within a biobank such as storage, use, dispersal, and disposal of human biological sample. It became necessary to coordinate the development of

national human biobanks in SA and beyond (Abayomi et al., 2013).

In June 2010, a joint project was launched by the National Institute of Health (NIH) and the Wellcome Trust called the Human Heredity and Health in Africa (H3Africa). The H3Africa project was targeted at identifying the genetic and environmental factors that affects common diseases in Africa and how to improve the health of the people. Fundamental to this project is the development of biobanks across Africa which will serve as storage for DNA and tissues, and essential medical information that can be accessed by local and international researchers. Several biobanks were established prior to the H3Africa project, but many did not adopt biobank best practices and legal and ethical guidelines on the storage of biological samples in SA (Abayomi et al., 2013). Biospecimen repositories in SA are created for numerous purposes and stimulated by various stakeholders that are typically academics, government and commercially driven. In spite of the burden of many diseases, much has been done to support the collection of biospecimens to accelerate biomedical discovery in South Africa. There are numerous biobanks in operation on a smaller scale in SA, yet access to information is limited and there is inadequate proof to show if they are fully compliant with quality standard procedures according to national and international biobanking best practices standard (ISBER, 2012). Developing a powerful LIMS for biobanks will allow samples to be processed much faster by reducing turnaround time and improving productivity by allowing test reviewers to work remotely to approve results.

Since biospecimens of large cohorts within the H3Africa project are sent to biobanks across Africa, efforts are being made to harmonise biobanking across Africa in order to maximise the use of biobank samples. Harmonisation of biobanks is associated with the issues of semantic interoperability through standardised message formats and controlled terminologies (Norlin et al., 2012). The Minimum Information about Biobank Data Sharing (MIABIS) ensures that the key information about a biospecimen is collected (Merino-Martinez et al., 2016). This process will catalyse underutilised biobank materials by harmonising numerous scientific results from various projects, using shared biobanked samples and data. This implementation of more workable centralised biobanks is developing gradually and yet to materialise.

2.2 Management of biospecimen data with other logistics

LIMS software supports biobanking tasks by managing the execution of tests on samples and tracks them through the testing process. Large amounts of samples are stored in various physical storages such as low-temperature freezers, nitrogen tanks and refrigerators. Thus the need for software to monitor the samples and link them to their various study donors (Schreier, 2008). Standard operating procedures (SOPs) are required to make sure that samples are prepared with proper quality control. The reliability of the underlying biological sample combined with the accuracy of the associated data is important for statistical interpretation in the context of epidemiological studies.

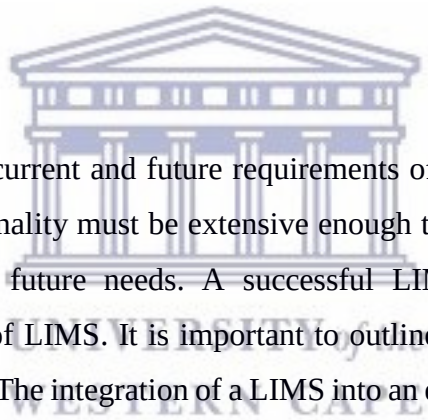
Biobanks are designed to manage the huge amount of data collected from humans. Management of, and linking between, patient samples and information drives the development and enhancement of LIMS software. LIMS also enables the integration to automation systems, by using the modern robotics solution to manage their samples and the clients request (Holbrook, 2008). Most times, the biological specimen collected does not follow specific standardised labelling procedures, with the result that samples are either kept in a freezer or corridor in a disarranged manner and not in compliance with the international quality management standards. It will be of tremendous benefit to develop SOPs at the level of collection, processing, management and storage of samples and associated data (Lund et al., 2007). LIMS also manages and controls the laboratory's workflow with the user input data, information collection, instrument integration, data analysis, user notification, conveying of information and documentation.

2.3 Challenges associated with sample data management and analysis procedures

In resource limited-settings, sample receiving and accessioning, processing, quality control and storage location are all captured manually. However, when a commercial LIMS is purchased, the operation may be restricted to a specific operation, which makes management of samples and data complex in a laboratory setting. The LIMS may have to manage a large volume of sample data and capture of valuable data with different sample preparation procedures, which often result in complex informatics and automation systems (Wigglesworth et al., 2012). The

design of a custom LIMS can be a way of solving the underlying issues. Even though a custom LIMS solution will not be developed from scratch in this thesis, the software components will be customised. For a LIMS development to succeed, it needs a team effort, and open source systems offer a platform for community development. The community gains from new functionality being sponsored by customers and by improvement of new features without additional costs, which will enhance the quality of the system (Puiggené, 2016). Another major challenge is the issue of researchers being unable to have access to appropriate samples and data quality which limits their research. Integrating samples acquired from multiple biobank centres is complex because each biobank centre may receive samples, store sample data using different standards. In an attempt to conform to a data standard to encourage sharing of data and samples across biobanks, a data standard has been proposed by Norlin and colleagues (2012) that determine the minimum amount of data that should be captured in a biobank.

2.4 **Selecting a LIMS**



The ability to understand the current and future requirements of a laboratory is crucial when selecting a LIMS. The functionality must be extensive enough to solve the current needs and flexible enough to meet the future needs. A successful LIMS implementation is often associated with the selection of LIMS. It is important to outline and examine the role of the LIMS within the organisation. The integration of a LIMS into an existing organisation structure could be a complex task to carry out (Tagger, 2013). However, if achievable, the developing of a custom LIMS solution will best fit the needs of the laboratory. The development of a custom LIMS can be accelerated by building or extending existing software components. The criteria used in selecting a LIMS are to:

a. Define the role of LIMS within the organisation and the major requirements

b. Consider how easily it allows integration of new instruments without complexity.

c. Examine the functionality that enhances productivity and quality management such as expiration date reminder, various test notifications and tracking of inventory.

d. Consider how supportive and helpful the technical support system is in providing assistance.

LIMS has come as a solution for managing the exponentially increasing data and are available both as open source and expensive commercial options (Tagger, 2013). There are numerous open source LIMS available which can be customised or tailored to suit the laboratory needs and communicate with the laboratory equipment for quality data management. There is no standard LIMS, they are acquired based on the attributes required by the laboratory (Zeliadt, 2013). The solution is provision of a LIMS to users, which they can customise and alter to their own need. This eliminates the need for the LIMS developer to incorporate specific functionality for different laboratories, but gives the LIMS users opportunity to produce their own by using agile software development methods which encourages enhancement and flexible response to change. There are issues arising in the development of LIMS standard operating procedures because the operations vary. Therefore, a degree of customisation is required to give the client the freedom to use different sample preparation options for the specific procedure used. This is common to data-entry systems, where a generic form is not appropriate (Tagger, 2013). Because of rapidly changing technology, the solution is to provide a LIMS to users, which they can customise and alter to suit their specific need.

It is important to select the functionality that matches the laboratory requirements. Many LIMS software are developed for a specific purpose. LIMS can be customised, ranging from application specific tools to multi-purpose solutions. However, the development of a LIMS system depends on how much customisation will be needed. The tailoring of the LIMS software may include changing report formats or changing menus. Yet other customisation will require new functions like interfacing with variety of instruments (Zeliadt, 2013).

However, selecting a LIMS for customisation requires knowing the advantages and constraints of the available software application. It is important to select the one that is best fit for the laboratory requirements. This could be achieved in various ways, such as by observing the demonstration of the usage of the software, by visiting the users' sites, demonstration of the process on-site, accessing the product documentation and the websites. Most of the time the software is purchased in modules or component, and then time is assigned for modification and customisation of the system. This permits the developer to add functionality according to the requirements specific to the laboratory. Thus, encourages a flexible solution to suit the specific purpose, and avoid the complexity of building a new LIMS system. Purchasing the software in modules or components could lead to complexity in the workflow processes (Paszko et al., 2001). In a resource-limited setting, there are various factors to be considered before selecting a LIMS. COTS software involves licence fees and cost of maintenance throughout its lifecycle,

and does not give users the flexibility to alter its functionality. Open source software is not free as well. However, it gives you control and flexibility. Despite availability of numerous open-source LIMS, they are unable to manage the needs of biobanks.

The major goals of this thesis were to implement two instruments import interfaces for DNA/RNA analysis concentration results, and configured Bika LIMS workflow to include sample preparation options for different sample preparation protocols.

Diverse open-source LIMS that have been used successfully in management of samples were reviewed. This helped us in choosing the best LIMS suited for the biobank requirement. Nine open source LIMS solutions were identified which include the following: OBiBa, OpenSpecimen, AGL-LIMS, Screensaver,HaIx, SIGLa, GnosisLIMS, Bika LIMS and OpenLIMS. Among the various open source LIMS listed, five open source LIMS were critically examined base on scope of the project, project activity and project status as options for biobanking functionality.

2.4.1 Development of AGL-LIMS for genotyping workflows in high throughput crop genotyping

Applied Genomics Laboratory (AGL-LIMS) LIMS is an open-source LIMS solution that specialises in the sample workflow associated with crop genotyping. AGL-LIMS was developed to solve the issue of samples failing at different steps of workflow due to the complexity in management of large scale data, causing the repetition of workflows (Jayashree et al., 2006). The software eliminates the process of each sample being reviewed several times. The AGL-LIMS was implemented with open-source software; the graphical user interface (GUI) and middle-ware have been implemented using Java Struts Framework technologies for management of medium to large scale plant genotyping data. The Tomcat Apache web server is used to provide GUI interconnections with the database (Figure 2).

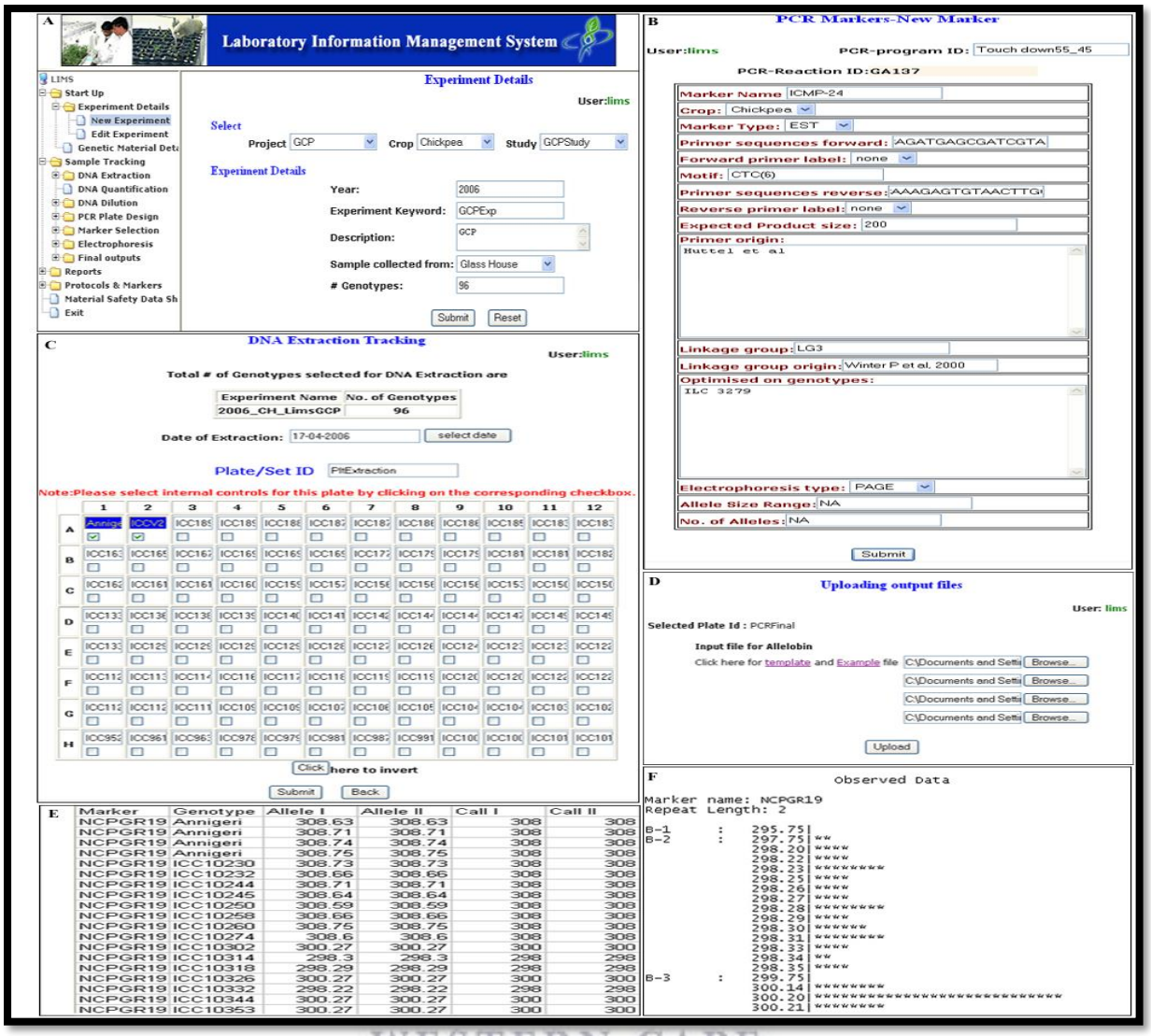


Figure 2: AGL-LIMS modules and user interfaces. A: The LIMS user interface for Experimental Design. B: Protocols and Markers – Form uploads for information on markers. C: Reports – sample DNA localization in microtitre plates for DNA extraction. D: Sample Tracking (Jayashree et al., 2006).

The application is designed as modules and is easy to learn and adopt. The system consists of four major modules which are:

(i) Experimental design that includes uploading files

(ii) DNA extraction and quantification

(iii) Generating reports

(iv) Data storage

AGL-LIMS has been implemented at the international crop research institute for semi-arid tropic (ICRISAT) which meets the needs of a moderately high throughput molecular genotyping resource. The AGL-LIMS was developed to capture high throughput simple-sequence repeat (SSR) genotyping data from the legume and cereal crops. The system monitors DNA and the data generated, with high throughput genotyping system using facilities such as Tecan Data, entered into the system via the use of forms for uploading of files (Jayashree et al., 2006). The application captures each step of the process from the start-up of the experiment procedure to the storing of data from the genotype detection step, hence, verifying that each data is handled in a similar way and all essential data are captured. However, AGL-LIMS has no sample tracking facilities to track all the details mentioned about the samples. Hence, leading to time wastage and limit efficiency in the management of sample reports. Moreover, there are no barcodes generated for the samples in the LIMS and no audit trail to show the source and events of records affected by any operation in the laboratory.

The AGL-LIMS provides a quality control in a medium scale genotyping laboratory, fulfilling various laboratory tasks, but information on DNA extraction, quantification and PCR protocols are entered manually through completion of a form. The development of instrument results file interface in the AGL-LIMS would allow for accuracy of the reported data, and getting the sample results into LIMS faster. However, the manual process of large volume of data entering into the LIMS and data review is time consuming and expensive. Probability of generating error is higher compared to executing it automatically.

2.4.2 Development of Open-LIMS for biological laboratories

Open-LIMS has been developed to fit the design for an organism independent project. It mainly supports the needs of biological laboratories working in functional genomics, particularly those in microarray and microscopy projects. The conception of the development of Open-LIMS came from the *Dictyostelium discoideum* functional genomics project team at the University of Cologne (Konertz, 2014). Open-LIMS is a web based LIMS built with Hypertext preprocessor (PHP) script language, MySQL an open-source relational database management system (RDBMS) and Java for services demons.

It was established on the concept of creating a function to support the user from the planning of experiment, running an experiment, entering and sharing data. The various functionalities include (Figure 3):

I. Sample management and tracking

II. Workflow management

III. Reporting and batching

IV. Barcode and audit trail

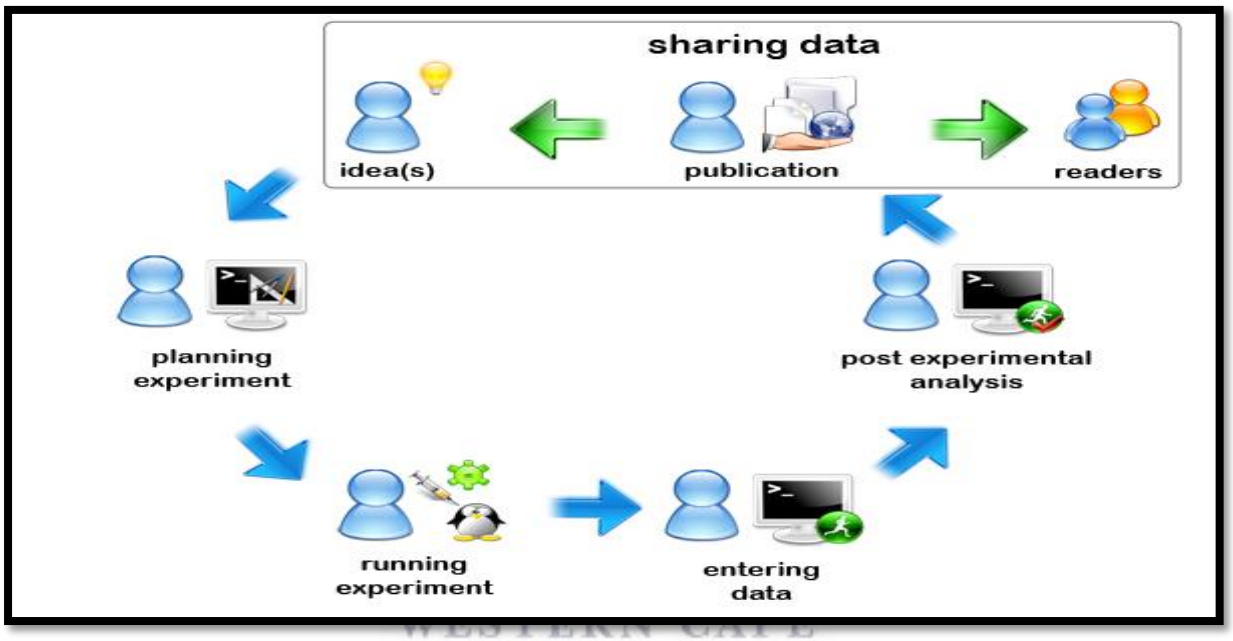


Figure 3: Open-LIMS Workflow design. The concept is based on a work-flow circle with different experiment phases to support the user from the planning of experiment, running an experiment, entering and sharing data (Konertz, 2014).

Open-LIMS allows instrument interfacing and files that can be uploaded to an Open-LIMS project. Open-LIMS has intuitive features with modular code and is extensive by design; however, they have less than seven user reviewers contributing to the software development as at the last update, indicating a very small community with only one contributor. The development is on and off and not functioning at the moment. There is no attached documentation and no demo server to demonstrate the software application. The Open-LIMS is quite premature; however, there is a chance to improve on the basic that has been built. The

software also requires an IT professional for the installation process. The last software release was over two years ago.

2.4.3 Development of OpenELIS for public health laboratories

OpenELIS is a web-based enterprise LIMS designed by the University of Iowa hygienic laboratory to accommodate and manage business processes that are related to public health laboratories such as clinical, new-born, and environmental animal samples. It was developed to provide an easier more stream-lined approach to retrieving information for clients and eliminate the use of multiple systems to complete tasks (OpenELIS, 2012). OpenELIS allows the clients to use the web browser to order tests, monitor samples and download results (OpenELIS, 2012). The software architecture was designed to accommodate future sample needs without a redesign. The technologies used to develop OpenELIS were Eclipse IDE for Java, Tomcat 5.5, and PostgreSQL 8.3. OpenELIS features include:

I. Sample and result entry
II. User management and administration
III. Role-based security
IV. Integration of Instruments
V. Data validation and reporting

OpenELIS has interface that parse files created by the instrument interface software and load the results into the appropriate worksheet, however the process was documented with limited information (Figure 4).

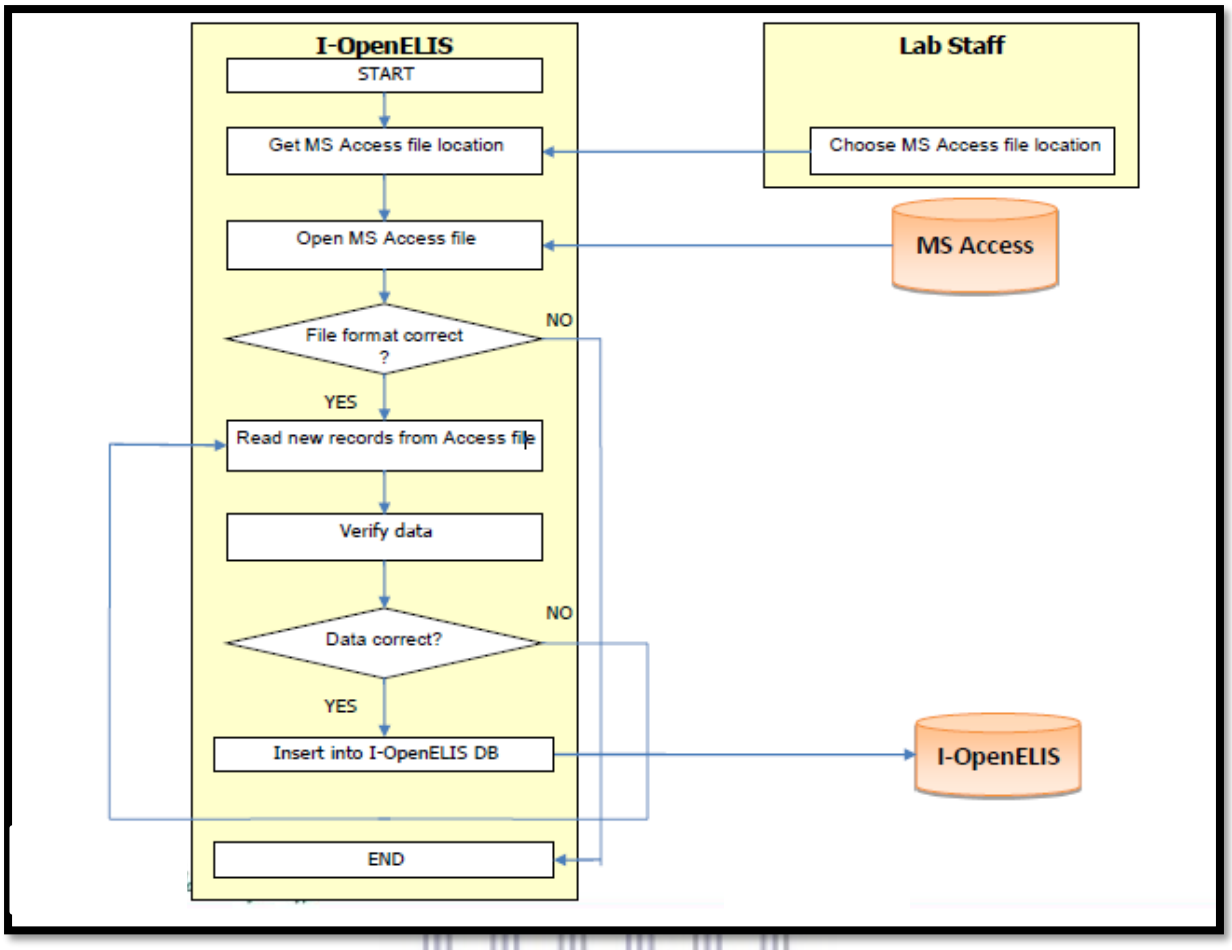


Figure 4: OpenELIS logic for importing of data. OpenELIS logic parse files created by the instrument interface software and load the results into the appropriate worksheet (OpenELIS, 2012).

The software maintains a common program code base, to ensure the LIMS application is more easily implemented by a greater number of the public health laboratories. Its LIMS project focuses more on supporting public health in their effort to improve the health of the human population, especially those vulnerable to diseases. OpenELIS has a global international community of developers and maintains contact with members through monthly conferences to address the needs, innovative solutions, enhancements and sharing of new application updates.

The project has been successfully implemented; however, OpenELIS documentation appears to be limited. The last update by the community of developers was three years ago.

2.4.4 OpenFreezer laboratory reagent tracking and workflow management system

OpenFreezer was developed to track information on rapid growth of large-scale DNA collections such as biospecimens, and specific properties of individual reagents including sequences and external identifiers that are crucial for systems-level biological approaches (Olhovsky, 2011). OpenFreezer is a web-based software application with a comprehensive and standardised documentation on typical laboratory reagents. OpenFreezer uses three-layer client-server software architecture, incorporating a MySQL database, PHP, HTML, JavaScript and Python programming languages (Olhovsky, 2011).

The modularity in design of OpenFreezer domain logic permits future customisation of existing components and addition of new modules. The system is sub-divided into three principal modules:

I. Reagent tracker
II. Location tracker
III. Administration

In location tracker modules, the module tracks the locations and properties of the physical preparations of reagents in the laboratory. The module has a container type for creating a new reagent type. A reagent may contain different "isolates" associated with its preparation. An isolate would refer to a specific colony pick. If different colonies are available, then each one of those picks would be an isolate numbered. For each reagent, a certain isolate is selected. If a particular reagent does not need isolates, then the container storing preparation of this reagent is marked (Figure 5). The lines allow one to select multiple selected isolates. Containers are grouped by container type that describes the type of reagents that can be stored in those containers, the storage medium of those containers, and attributes associated with the preparations in those containers for example are glycerol stocks', 'cell Line', and ' DNA'.

Figure 5: Creating and modifying container types in OpenFreezer. Containers are grouped by container type that describes the type of reagents that can be stored in those containers, the storage medium of those containers, and attributes associated with the preparations in those containers for example are glycerol stocks', 'cell Line', and ' DNA'. (Olhovsky, 2011).

OpenFreezer tracks over 150,000 reagents and used by over 150 users from 13 different laboratories at the Samuel Lunenfeld Research Institute in Canada (Olhovsky, 2011). OpenFreezer is well structured, documented and a simplified system; however, the system has inadequate functionality, thus rendering it immature. The software lacks essential features used in today's LIMS technology such as file management, barcoding, labelling and instrument interfaces.

2.4.5 Bika LIMS

Bika LIMS is a web based open source LIMS developed in 2002 as a prototype, for management of laboratory information in the wine industry (Bika, 2016). The system has since seen a remarkable growth with major releases in water quality management and inter-laboratory proficiency testing. Bika LIMS modularity allows for customisation and implementation in any laboratory, from small to large research and clinical laboratories (Bika, 2016). The system was written in Python, built with modern application server and content management system frameworks Zope and Plone. Bika benefits from Zope and Plone role based security, workflow, audit trails and integrated alerts. Bika LIMS features include:

I. Sample tracking, analysis requests and worksheet
II. Batching by project or case
III. Sample storage
IV. Analysis prioritisation
V. Pending task alerts
VI. Results invalidation and retesting workflow.

Bika LIMS workflow incorporates from management of analyses requests and track analyses results to verification and publication (Figure 6). A client of the laboratory is represented as "client contacts" in the system and is registered as a user with password verification. The workflow starts with the completion of analysis request online form when the samples are ready to be transported to the laboratory for analyses .The client log-in to the system, checking all the analyses required for the procedure. After submission of the form, a request is signified with the status sample due. The lab clerk receives a notification on the system when the sample arrives in the laboratory. The workflow process continues when samples are received in the laboratory by capturing data into the worksheet. If an error is detected in the verification step, there is a procedure to enforce correction by the lab manager by retracting the results for retesting before publication. Samples in the laboratory could be tracked throughout the procedure by the client, but the results can only be seen if it had been verified. The results are published to the contacts via publication preference which had been set in advance, usually through email (Bika, 2016).

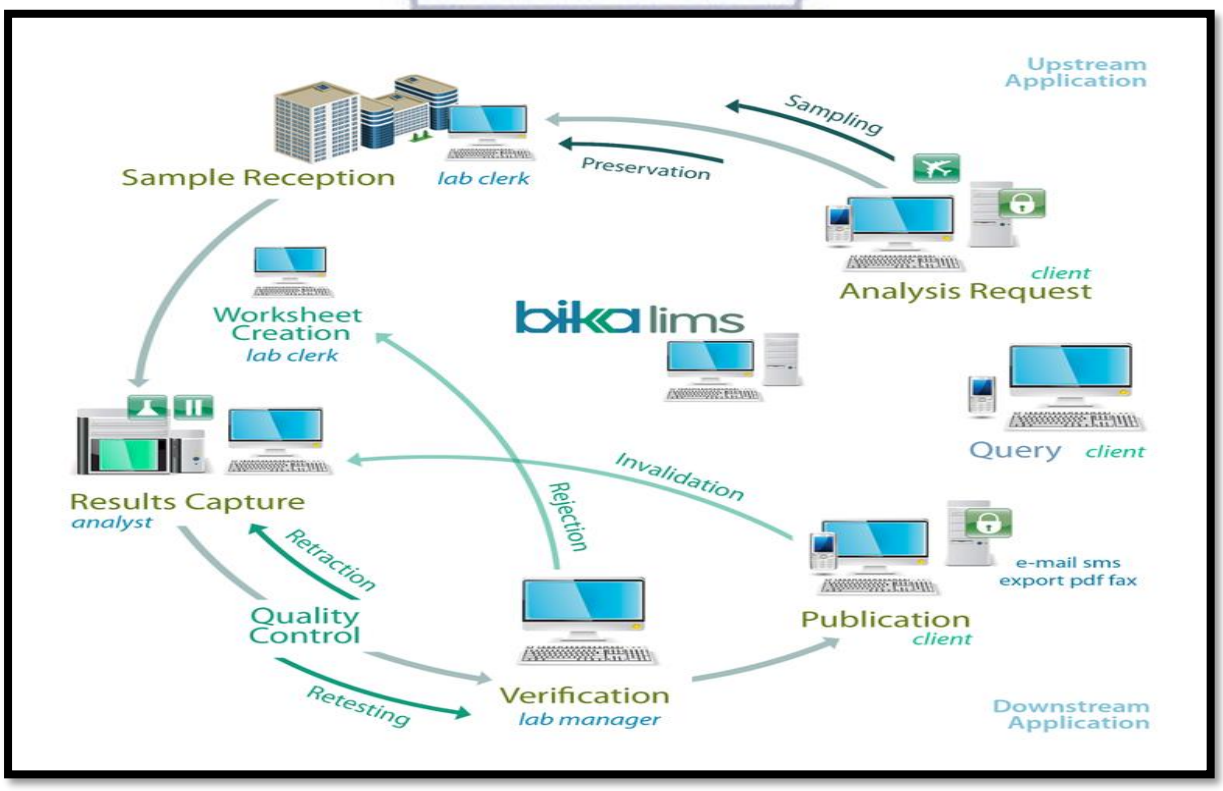


Figure 6: Bika LIMS workflow. The system manages and tracks the lifecycle of the sample from the time it is received at the biobank to the time that the sample is stored or shipped. Powerful document management and capacity building tools are available to support laboratories based on the content management features inherited from the Plone framework (Bika, 2016).

Designing the LIMS required considering other systems in the laboratory that must interface with the LIMS. This includes various data systems like Chromatography Data System (CDS), and electronic lab notebooks (ELN) systems that may be attached or run independently. Also, analytical data can be transferred by (Dubey et al., 2006).

I. Data capture from an instrument with analyses results by the attached data system and only a result is transferred to the LIMS.
II. Capturing results and transferring to the LIMS via a Scientific Data Management System.
III. Manually entry into the LIMS or captured electronically via an Electronic Laboratory Notebook (ELN) and transferred electronically to LIMS.
IV. Capturing electronically through mechanism such as file parsers.

In this project, instrument analyses results generated by the biomedical laboratory was captured into Bika LIMS through instrument import interface by uploading the CSV file via USB drive Qubit Fluorometric and. BioDrop µLITE instrument results file are in CSV format. The task was not on

I. Interfacing devices with LIMS
II. The development of an interface between devices
III. Interchange of the data.

2.5 Summary

The key to customisation of a LIMS for human biobank is utilizing open source LIMS software that has the best fit for laboratory requirements. Bika LIMS has already been used in different laboratories for management of various samples compared to other open source software reviewed in this project (Table 1). Bika LIMS was designed in such a way that allows further customization with modularity of code.

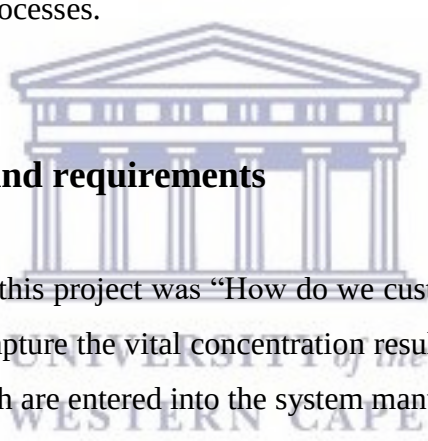
Table 1: Open source LIMS review and consideration. The pros and cons of the reviewed open source LIMS in a low-resource setting.

LIMS Open source Software	Pro	Con
AGL-LIMS	The application was designed as modules with easy to adopt methods in ensuring that every DNA sample is handled in an identical manner and all the necessary data are captured	AGL-LIMS has no sample tracking facilities to track all the details mentioned about the samples. Forms only allow the user to enter concentrations data manually, no bar code label to track sample
Open-LIMS	Open-LIMS allows instrument interfacing. Open-LIMS has intuitive features with modular code	The software requires an IT professional for the installation process. Limited documentation
OpenELIS	It has instrument interface logic created for parsing files	Limited documentation on interface software and load the result
OpenFreezer	OpenFreezer is well structured, documented and a simplified system for specific sample prep customisation	The system has inadequate functionality, thus rendering it immature without barcode labelling and instrument interfaces.
Bika LIMS	Allow instrument import interfaces. Customisable workflow for sample management. It has been used in many laboratories.	Not been used in the biomedical field before

3 Methodology

We consider an open-source system which already fulfils major aspects of the LIMS requirement to cater for human biospecimens. Bika LIMS was adopted for the project which already fulfils certain clinical subject requirements. The LIMS will accommodate data from BioDrop μLITE and Qubit Fluorometric instruments for usage in the biomedical field. This will support daily automatic importing of Biodrop and Qubit Fluorometric results into the LIMS by eliminating redundancy in the laboratory and specification of sample preparation options protocol used. Tygerberg haematology pathology department uses Qubit Fluorometer and BioDrop μLITE instruments for DNA/RNA quantification and results are captured manually.

In the sections, we discuss the strategies that were used to develop the interfaces, customise the workflow and verify the processes.



3.1 Research question and requirements

The research question driving this project was “How do we customise Bika LIMS for human biobanking to automatically capture the vital concentration results from the samples analysed and manage sample data, which are entered into the system manually at Tygerberg biobank?”

This led to the project requirements on how to support BioDrop μLITE and Qubit Fluorometer instruments; so that concentration results from DNA/RNA analytical data are stored directly into the LIMS to eliminate transcription and typographical errors. And also to specify the preparation workflow options used physically to manage human samples in the pathology laboratory.

3.2 Methods

3.2.1 Process description

When human samples are received, a set of analysis requests was set up for analysis to be carried out. In Bika LIMS, "Analysis Request" sample preparation options for preparation of DNA/RNA analyses was incorporated in the form. This links each sample with the "sample preparation option" to be used in the preparation and the associated information to be included in the workflow. After sample preparation is done by the analyst, BioDrop µLITE or Qubit Fluorometer instruments are used to analyse and determine the DNA/RNA concentration. The instruments generate results files. The results data files were saved on a pc via USB stick and can be easily imported to LIMS through the new import interface. The results were automatically added to the workflow indicating the physical method used, which are being managed in the LIMS where the results are verified and published (Figure 7).

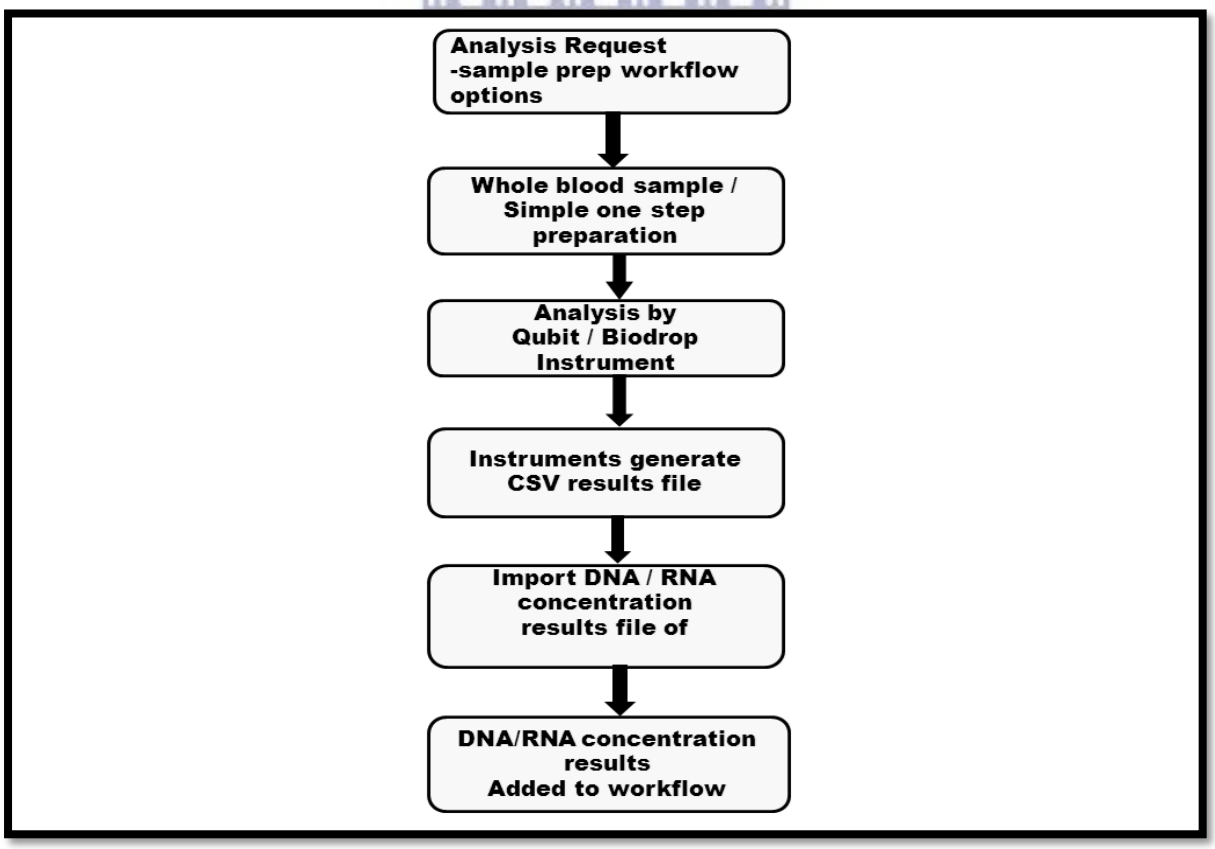


Figure 7: The process description: From analysis request in Bika LIMS, a sample preparation option can be chosen to indicate preparation workflow option used. The instruments generate CSV results file which were imported into the LIMS through the user import interface. The results will be managed by the Bika LIMS.

The first task was to write and integrate into the LIMS a parser that can read the file and enter automatically the result into Bika LIMS. Bika LIMS workflow starts with the "Analysis Request"; clients request a specific analysis to be done on a patient sample that has to be prepared using a given workflow. The current Bika LIMS version does not provide a way to select the workflow to follow during the preparation. Tygerberg biobank uses different workflows to prepare the sample for analysis.

The second task was adding a "selection field" client can select the workflow. A label preparation workflow option was created with two sample preparation options fields named whole blood, and "simple one step preparation" option.

The third task was performing alpha testing on the entire system by one of the technical team.

After preparation of the sample using the client selected workflow, the sample will be analysed with one of the laboratory instruments. BioDrop μLITE or Qubit fluorometer instruments was used for analysing of DNA/RNA human specimen (Figure 8).

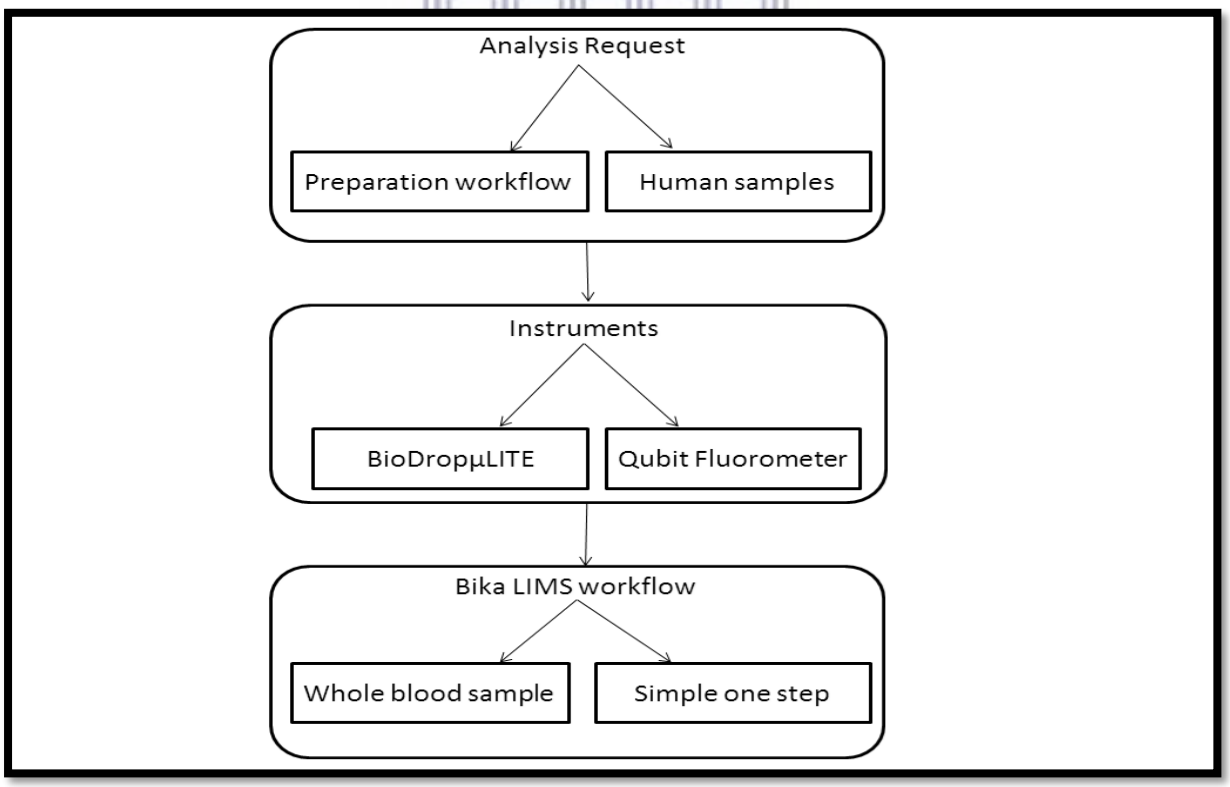


Figure 8: The preparation workflow options and laboratory analyses. In "Analysis request" preparation workflow was included to specify the workflow option used physically and human sample to include the method of lab analyses. The instrument import interface for BioDrop μLITE/Qubit fluorometer was added and results imported and managed in Bika LIMS by the workflow.

The “Analysis Request” form specifies the client request for analyses to be done; hence, it must include the workflow option used in preparation. Also, the sample preparation option used must be linked with type of laboratory analysis process for human specimen.

3.2.2 Waterfall software engineering

The project was carried out using waterfall software engineering approach with a straightforward process. The development method allows alterations early in the life cycle. Since the phases are precise, one phase is done at a time. It involves the determination of the exact requirements for the system. Requirements are gathered by:

I. Interviewing the Tygerberg pathology work groups
II. Observing employees doing their jobs
III. Reviewing documents

The reason for choosing waterfall is because the requirements are known, clear and fixed. The model emphasizes planning in the early stages and catches design flaws before they develop. Also, it works well for projects in which quality control is crucial. For many years the most tried and true as well as the most popular LIMS implementation style was the waterfall methodology (CSolsinc, 2017).

3.3 Applying the methods

This segment clarifies the outline standards behind Bika LIMS interface modules alongside standard architecture and functions for creating a specific instrument interface. Bika LIMS was designed to create a platform where a variety of instruments can be integrated. It has built-in generic parsers that make it possible to develop parsers for file types. The architectural concept used in creating an instrument import interface is represented in a flowchart (Figure 9). By designing a flowchart from the process used in Bika LIMS instrument interface for other laboratories, will refine and give steps that will support creating a new instrument import interface to accommodate human sample data. The logic applied in importing analyses results from the instruments include using sample ID and analyses keywords in the import file, and matching them with those of the analyses services and analyses requests, by using the

keywords of the analyses that set up the analyses configuration. The design helps to virtualise the logic and process that was used in creating instrument import interfaces for BioDrop µLITE and Qubit Fluorometer.

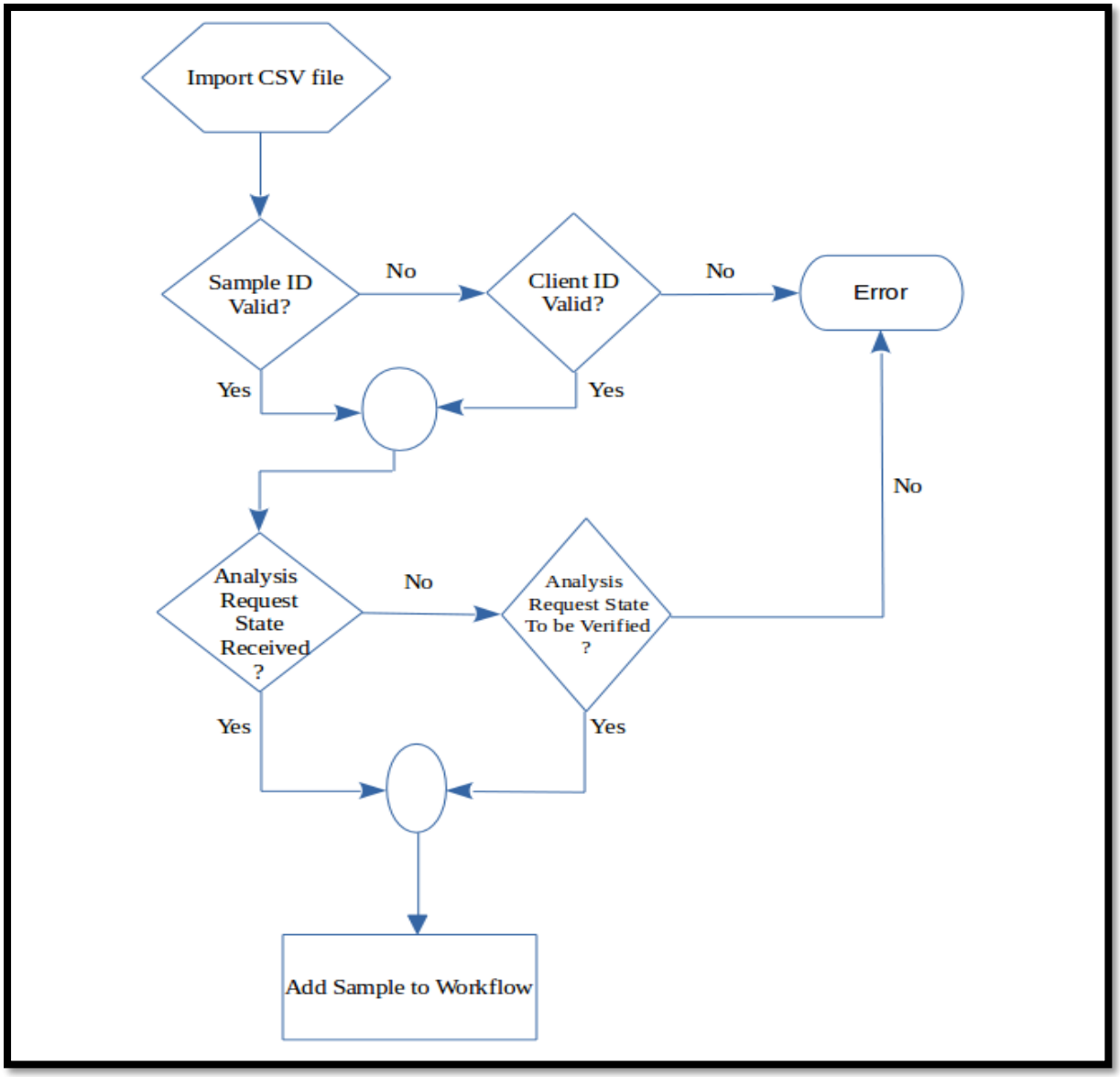
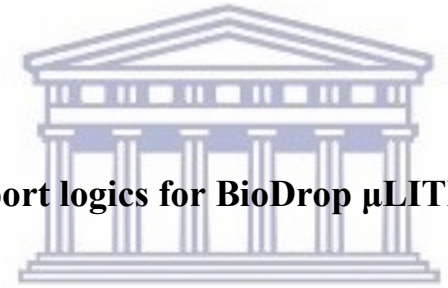


Figure 9: Flowchart summarising the steps involved in importing analyses results. DNA concentration result data file in CSV format are imported.The logic used sample ID or client ID to match the "Analysis Request" sample ID or client ID . If the sample ID or client ID is valid, the outstanding fields will update information on each specific sample, because all samples have unique ID. An error is generated if sample ID and client ID does not exist. Analyses requested must also be in received state or to be verified state for the data to be imported, if not, an error message is generated. The analyses results are imported if all the functions are fulfilled.

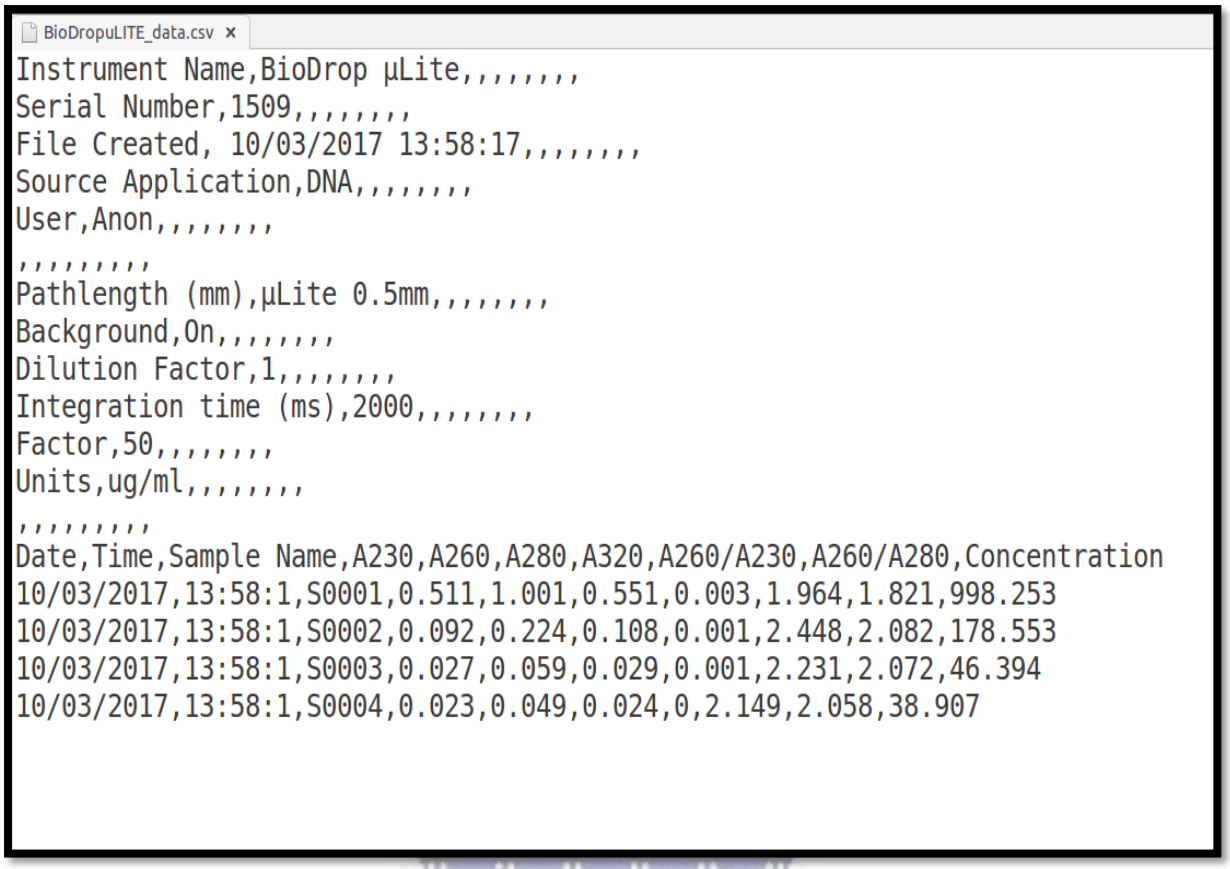
3.3.1 Creating an instrument import interface for BioDrop µLITE and Qubit Fluorometer

The instrument import logic was designed by creating a template, parser and controller classes for BioDrop µLITE and Qubit Fluorometer. The instrument "result file interface" is a code that parses and imports the results from those instrument-specific files into Bika LIMS. The concentration results generated from BioDrop µLITE and Qubit Fluorometer from analyses of DNA/RNA is in CSV file format but different structure, hence each import interface must be developed specifically for each result file structure. The data generated from the instruments was saved and transferred using a USB. The instrument import logic used and the related classes are part of the bika.lims.exportimport.instruments package. This package consists of main classes involved in parsing and importing results.



3.3.2 Creating import logics for BioDrop µLITE instruments results file

Development of an import interface by design starts with creating a template for BioDrop uLite. BioDrop µLITE instrument results file is generated from the instrument data in CSV format (Figure 10). TAL is a Plone template language, which is an XML based language that adds programming logic to XML attributes. Python parsing expression allows the input of code directly in the template.



BioDropuLITE_data.csv

```
Instrument Name,BioDrop µLite,,,,,,,,
Serial Number,1509,,,,,,,,
File Created, 10/03/2017 13:58:17,,,,,,,
Source Application,DNA,,,,,,,
User,Anon,,,,,,,
,,,,,,,,,
Pathlength (mm),µLite 0.5mm,,,,,,,
Background,On,,,,,,,
Dilution Factor,1,,,,,,,
Integration time (ms),2000,,,,,,,
Factor,50,,,,,,,
Units,ug/ml,,,,,,,
,,,,,,,,,
Date,Time,Sample Name,A230,A260,A280,A320,A260/A230,A260/A280,Concentration
10/03/2017,13:58:1,S0001,0.511,1.001,0.551,0.003,1.964,1.821,998.253
10/03/2017,13:58:1,S0002,0.092,0.224,0.108,0.001,2.448,2.082,178.553
10/03/2017,13:58:1,S0003,0.027,0.059,0.029,0.001,2.231,2.072,46.394
10/03/2017,13:58:1,S0004,0.023,0.049,0.024,0,2.149,2.058,38.907
```

Figure 10: BioDrop µLITE instrument data file format and structure. The readings of spectrophometric absorbanceat at A260,A280 and A230 (nm). The reading at A260 is used by the software to automatically calculate the DNA or RNA concentration in(ng/ul). Protein levels are measured at A280, and this together with the A230 value, is used to identify any contamination of the sample. The concentration information must be transfer into the LIMS.

The "file" field is used for "input type of element for results file upload". This is the file formats and file versions field that Bika LIMS accepts for this instrument and model. If the results file specifications change in future, there is always an upgrade for implementation, so that for a given instrument, more than one format will be available. "Analysis Requests" state, allows the user to set the results and they must only be saved if their analysis request have the state "received" or "received and to be verified". "Results override" field allows the user to set the rules the importer will follow if a result has already been set in the system. The flowchart (Figure 11) represents the logic behind importing the result values from BioDrop µLITE instrument. The *Importer* parser ignores all the data until it finds a header that starts with date, but if the header starts with some other type of data, an error will be generated. If the header starts with date, it next function checks if the number of rows equal number of headers to make sure there is no blank header and check if the data row is longer than the header row. If the

header and the row numbers are not equal, an error is generated. The next step split the lines and retrieves the data. The controller then executes the importer for the submission of the human sample data.

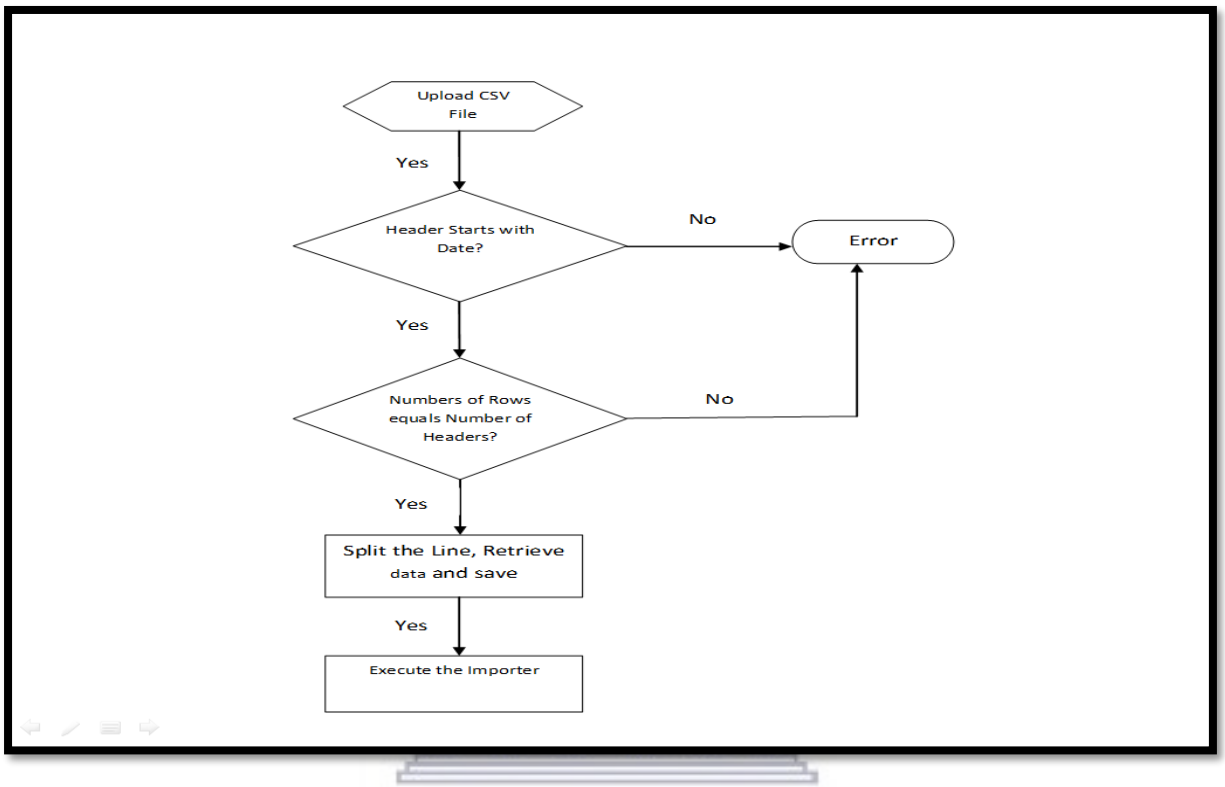


Figure 11: Logic used for importing result data from BioDrop µLITE instrument data file. Flowchart depicting the logic behind importing data from the BioDrop µLITE instrument result file using the header to set the flag.

Subsequently, a parser is then created for BioDrop µLITE, the BioDropCSVParser is the class responsible for parsing the results file. The parser class inherits from *InstrumentResultsFileParser* or from any of its child classes and overrides its methods. *InstrumentCSVResultsFileParser* is the most commonly used class to be inherited from, which is a child from *InstrumentFileParse*r. As the name indicates, this class provides methods to read and parse instrument data.

The *__init__ (self, csv, analysis key)* method in the parser class, searches for the headline-line beginning with "date" and set the flag to signal where the actual data is (Figure 12), once the flag is set, all the following lines after "date" are real values.

```
def __init__(self, csv, analysiskey):
    InstrumentCSVResultsFileParser.__init__(self, csv)
    self.data_header = None
    self.file_header = {}
    # Set this flag when we find the header-line beginning with "Date,"
    # Once this flag is set, all following lines are real data.
    self.main_data_found = False
    self.analysiskey = analysiskey
```

Figure 12: Method used for parsing instrument data file BioDrop µLITE. The function set the flag, that is a special mark where actual data are. It inherited from the *instrumentCSVResultsFile* Parser class and it provides methods to read and parse instrument data.

The *BioDropCSVParser* class inherited from *instrumentCSVResultsFile* class the override the *_parseline (self, line)* method which is functional for user importer interface to read and parse CSV file. The parent class called this method every time a new line is reached. The logic in this method must be able to split the line, retrieve the data, fill a key and value dictionary. The analysis service keyword and the keys from inner dictionary are the result and values to be saved for the analysis. According to default set up, the importer will use the field defined by the default result key as the default value for the analysis. However, the importer will search for the other values to find matches with temporary field. The parser classes are usually defined inside the *__init__.py* from that package.

The controller (Figure 13) handles the submission of the template by obtaining the request values, and setup parser to be used for the particular file before executing the importer.

```
""" BioDrop uLite
"""
from bika.lims import bikaMessageFactory as _
from bika.lims.utils import t
from . import BioDropCSVParser, BioDropImporter
import json
import traceback

title = "BioDrop uLite"

def Import(context, request):
    """ Read biodrop analysis results
    """
    infile = request.form['filename']
    fileformat = request.form['format']
    artoapply = request.form['artoapply']
    override = request.form['override']
    sample = request.form.get('sample', 'requestid')
    instrument = request.form.get('instrument', None)
    errors = []
    logs = []
    warns = []
```


Figure 13: The controller class for BioDrop µLITE instrument data file. The controller declares the instrument title and manages submission of the template created by declaring the BioDrop µLITE instrument title, and using *import (context, request)* method to add the input file into the LIMS.

The controller class constitutes the method that will be launched when the user submits the form. Moreover, a global variable called title must be declared. The title will be used on instruments selection list for the specific form provided. *The importer Process ()* does all the work by running the parser and saving the data retrieved into Bika LIMS. The controller class is defined inside the µLITE.py file.

The final step is registering of interface in the system by adding the path to the new package in *bika.lims.exportimport.instruments.__init__.py* (Figure 14).

```
import sys
import inspect

from generic import xml
from agilent.masshunter import quantitative
from foss.fiastar import fiastar
from foss.winescan import auto
from foss.winescan import ft120
from thermoscientific.gallery import Ts9861x
from thermoscientific.arena import xt20
from panalytical.omnia import axios_xrf
from alere.pima import beads, cd4
from lifetechnologies.qubit import qubit
from biodrop.ulite import ulite
from tescan.tima import tima
from sysmex.xs import i500, i1000
from beckmancoulter.access import model2
from rochecobas.taqman import model48

__all__ = ['generic.xml',
           'agilent.masshunter.quantitative',
           'foss.fiastar.fiastar',
           'foss.winescan.auto',
           'foss.winescan.ft120',
           'thermoscientific.gallery.Ts9861x',
           'thermoscientific.arena.xt20',
           'panalytical.omnia.axios_xrf',
           'alere.pima.beads',
           'alere.pima.cd4',
           'lifetechnologies.qubit.qubit',
           'biodrop.ulite.ulite',
           'tescan.tima.tima',
           'sysmex.xs.i500',
```

Figure 14: Registering the BioDrop µLITE interface. BioDrop µLITE interface is registered by adding the path to the new package.

The life technology instrument imports file Qubit Fluorometer file format, and the structure (Figure 15) is different and works differently compare to the BioDrop µLITE instrument.

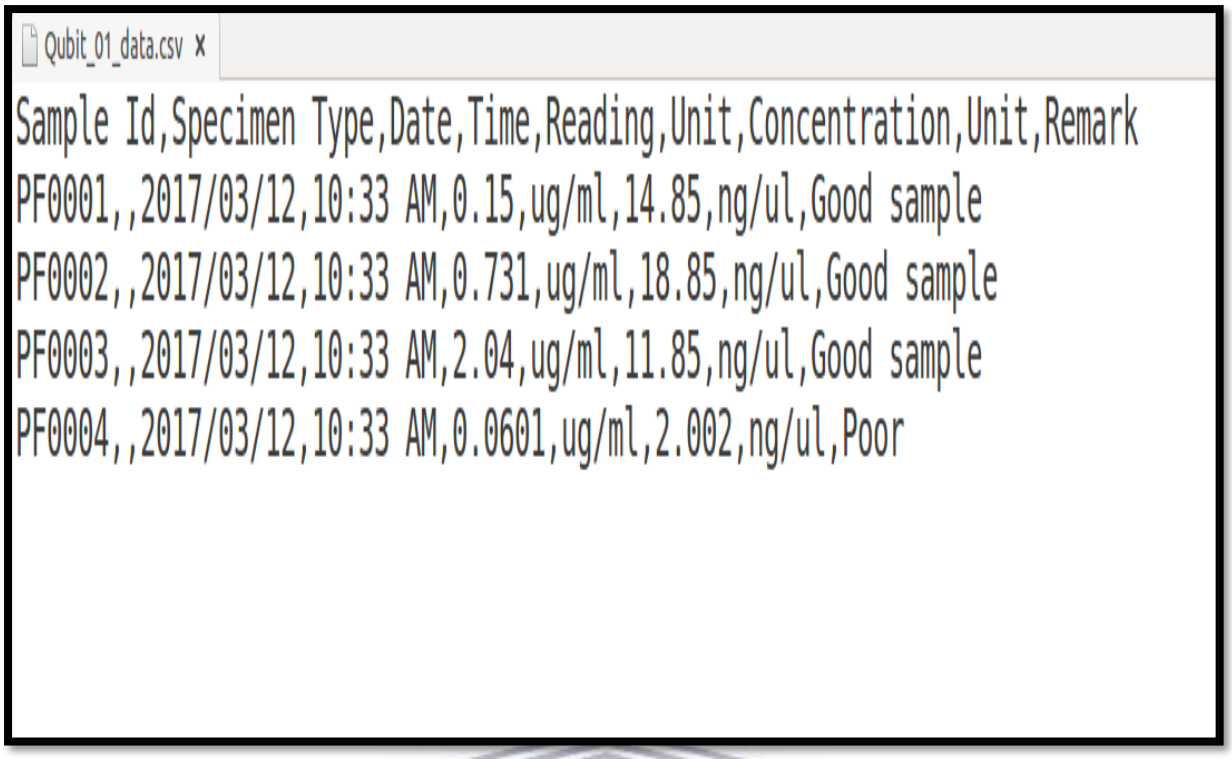


Figure 15: Qubit Fluorometer instrument data structure and format. The output of the Qubit Fluorometer instrument data (Qubit_01_data.csv) in CSV file format and the structure, the concentration results analysis data must be captured into BikaLIMS.

3.3.3 File import logics for Qubit Fluorometer instruments results

Template for life technology is designed similar to BioDrop μLITE by using TAL for instrument import form to create an interface to import the results. Life technology import interface consist of fields such as result file upload, file format field usually in CSV or TSV and instrument that allows the user to set the instrument to which the results will be linked if the file contains calibration tests. The flowchart (Figure 16) represents the logic behind importing human sample data from the Qubit Fluorometer instrument. After the results file was uploaded checks if the data starts with sample ID for the process to proceed. If the line does not start with the sample ID, then an error is generated. The next step renames one header if the names of two headers are identical. The parser parses the results file, and the importer imports all the data by saving the data retrieved into Bika LIMS.

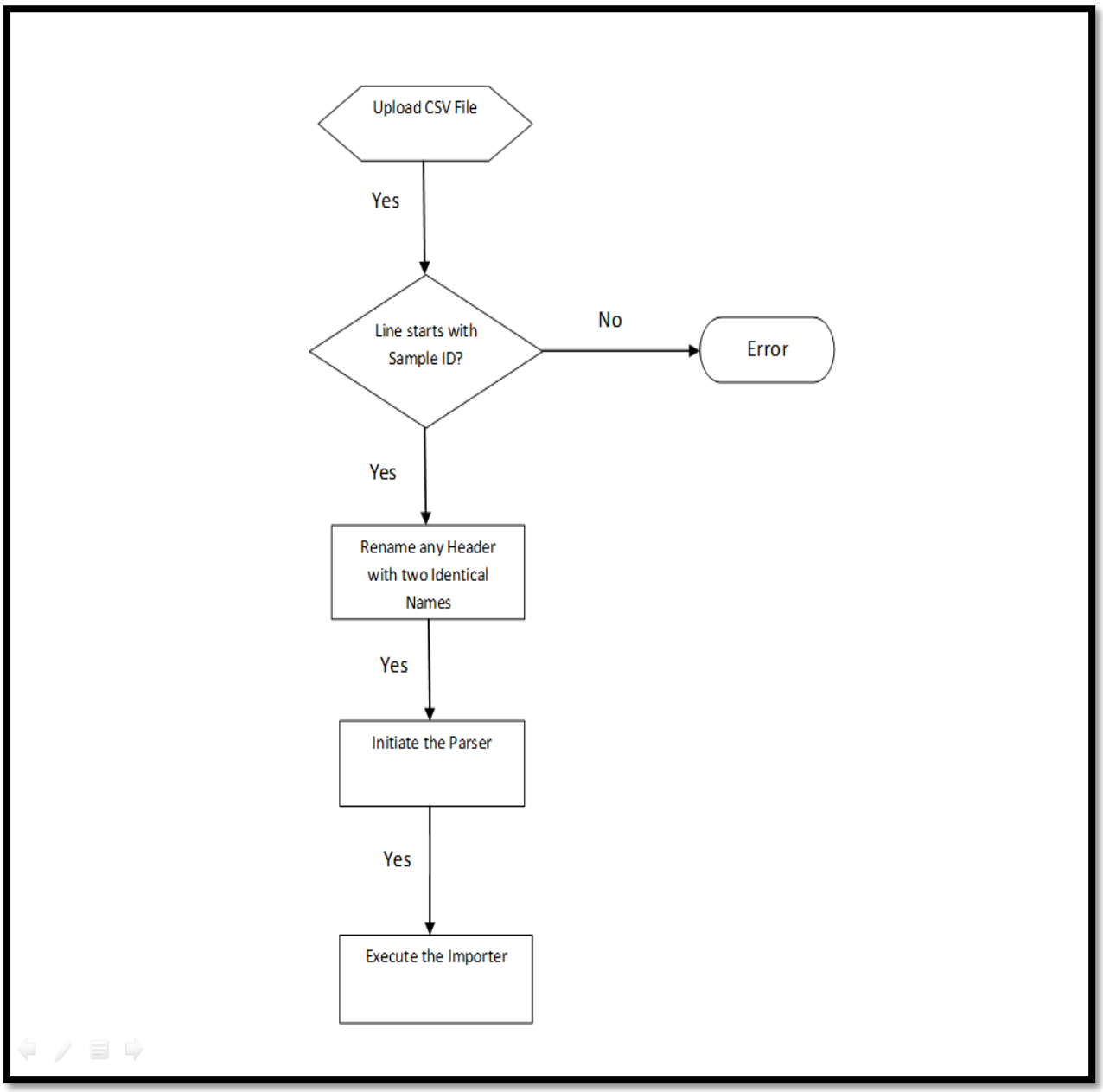


Figure 16: The logic used for importing data for Qubit Fluorometer result file. The logic checks if the data starts with sample ID for the process to proceed,with the initialising and execution of the importer.

The Qubit parser class is defined inside in the __init__.py file package. If the lines start with the sample ID, the method splits the line from the input CSV file, retrieving the data and fills a key, value dictionary (Figure 17).

```
def _parseline(self, line):
    # Sample Id,Specimen Type,Date,Time,Reading,Unit,Concentration,Unit,Remark
    if line.startswith('Sample Id'):
        self.headers = [token.strip() for token in line.split(',')]
        self.headers[7] += '1'  # Two identical header, rename one of them.
        return 0

    # WW-01176,Blood,2010/11/02,10:33 AM,0.15   ug/ml,10.85,ng/ul,Good sample
    # WW-01175,Plasma,2010/11/02,10:33 AM,0.731 ug/ml,10.85,ng/ul,Good sample
    splitted = [token.strip() for token in line.split(',')]
    _values = dict(zip((self.headers),(splitted)))

    values = {self.analysiskey:
              {'DefaultResult': 'Concentration',
               'Remarks': _values['Remark'],
               'Concentration': _values['Concentration'],
               'Reading': _values['Reading']}
             }
```

Figure 17: Method used to retrieve data from Qubit Fluorometer data file. The Importer used the parser function by locating the field specified by the default result key, and utilised it as the default value for the analyses.

A controller is created in qubit.py file to manage the submission of the results of the template by acquiring the request values and also initialising the parser, and execute the importer, which carry out the execution by running the file parser and saving the data retrieved into Bika LIMS (Figure 18).

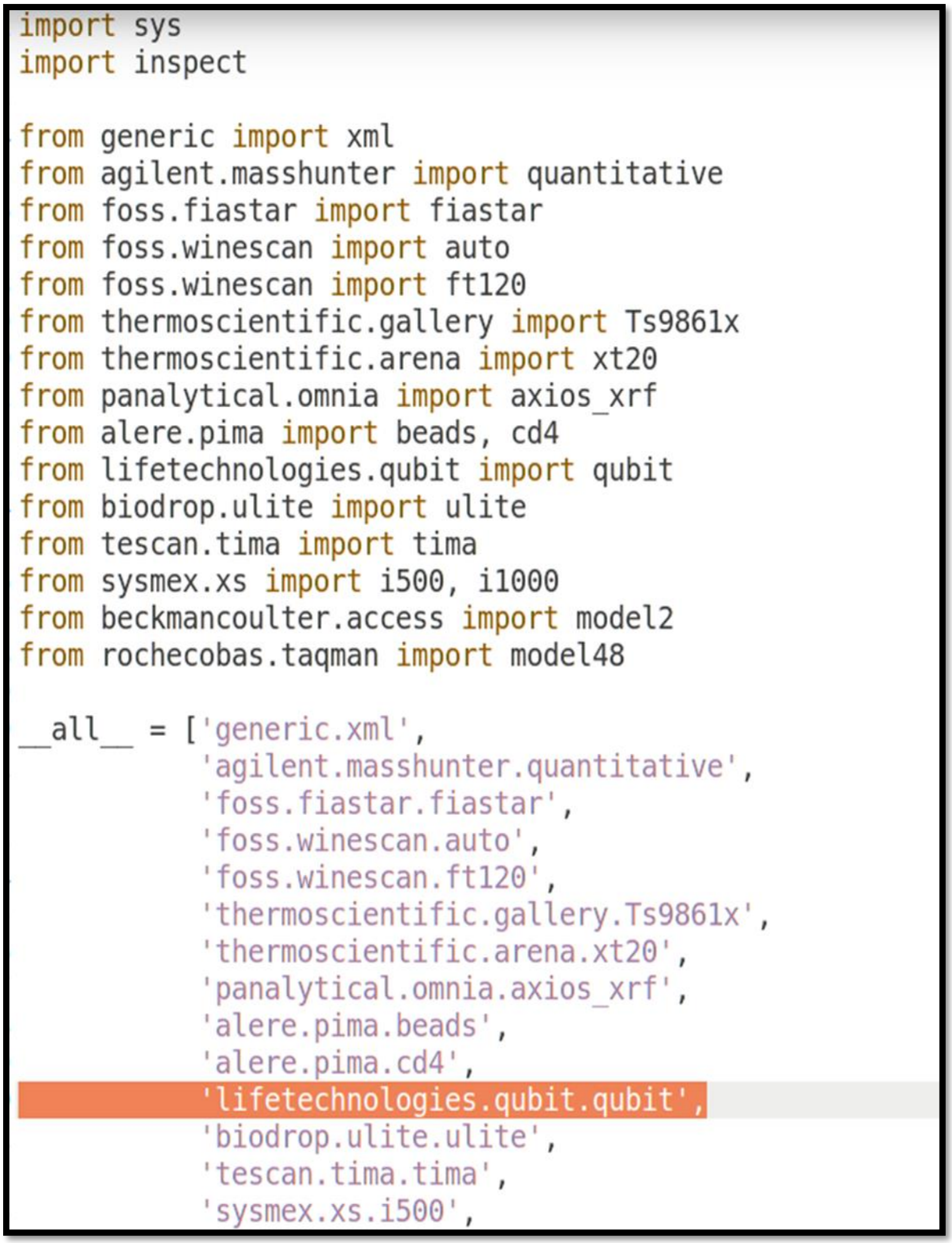
```
    importer = QuBitImporter(parser=parser,
                             context=context,
                             idsearchcriteria=sam,
                             allowed_ar_states=status,
                             allowed_analysis_states=None,
                             override=over,
                             instrument_uid=instrument)

    tbex = ''
    try:
        importer.process()
    except:
        tbex = traceback.format_exc()
    errors = importer.errors
    logs = importer.logs
    warns = importer.warns
    if tbex:
        errors.append(tbex)

results = {'errors': errors, 'log': logs, 'warns': warns}
return json.dumps(results)
```

Figure 18: The controller declares the instrument title and manages submission. The controller manages the submission of the template into the LIMS.

The last step is registering the life technologies qubit import interface into the system (Figure 19).



```
import sys
import inspect

from generic import xml
from agilent.masshunter import quantitative
from foss.fiastar import fiastar
from foss.winescan import auto
from foss.winescan import ft120
from thermoscientific.gallery import Ts9861x
from thermoscientific.arena import xt20
from panalytical.omnia import axios_xrf
from alere.pima import beads, cd4
from lifetechnologies.qubit import qubit
from biodrop.ulite import ulite
from tescan.tima import tima
from sysmex.xs import i500, i1000
from beckmancoulter.access import model2
from rochecobas.taqman import model48

__all__ = ['generic.xml',
           'agilent.masshunter.quantitative',
           'foss.fiastar.fiastar',
           'foss.winescan.auto',
           'foss.winescan.ft120',
           'thermoscientific.gallery.Ts9861x',
           'thermoscientific.arena.xt20',
           'panalytical.omnia.axios_xrf',
           'alere.pima.beads',
           'alere.pima.cd4',
           'lifetechnologies.qubit.qubit',
           'biodrop.ulite.ulite',
           'tescan.tima.tima',
           'sysmex.xs.i500',
```

Figure 19: The registration of the life technology instrument interface. It registers the instrument interface by adding the path to the package.

3.3.4 Customisation of Bika LIMS for workflow preparation option

Bika LIMS uses DC Workflow which is a tool developed for building a workflow, and it is also a product of Zope content management framework to provide fully customisable workflows for the CMF portal_workflow tool (Figure 14).

The sample preparation interface is defined in Zope interface to enable the “sample_prep” workflow fit into an object's workflow chain used by the Bika workflow objects to make aware of the sample preparation workflows options. The “analysis” and “sample” workflows were updated, thus, “simple one step” and “whole blood preparation” options method were added to the default workflow file. Hence, permitting Bika LIMS default workflow to be set-up for sample preparation workflow in the Plone panel. Then the Zope management interface for sample preparation was accessible from the Plone portlet, which are pluggable user interface components. Bika LIMS workflow was customised for sample preparations workflow options in a single transition. It was created by clicking on the portal_workflow link, and adding the preparation workflow option name (figure 21). The sample preparation workflows options created is only an option to choose from the variety of sample preparations workflows used in preparing the samples. The workflow manages the samples and the information linking it with the results. The workflow does not have the different preparation methods steps for now.

In “Analysis Request”, which contains analysis instances, sample preparation options functionalities were created to read the "string field” which gives permission to modify the portal content, made it visible and also linked the associated information in Bika LIMS with the option used. This was coded by using the technology Zope server component, Plone content management framework and Python programming language. The function will return a list of sample preparation workflows. These were identified by scanning all the workflows IDs for those beginning with "sampleprep" in "portal_workflow" and allow for appending of workflow title. This flag enables the sample_prep workflow transitions to be inserted into an object's workflow chain. The code supports the additional workflows.

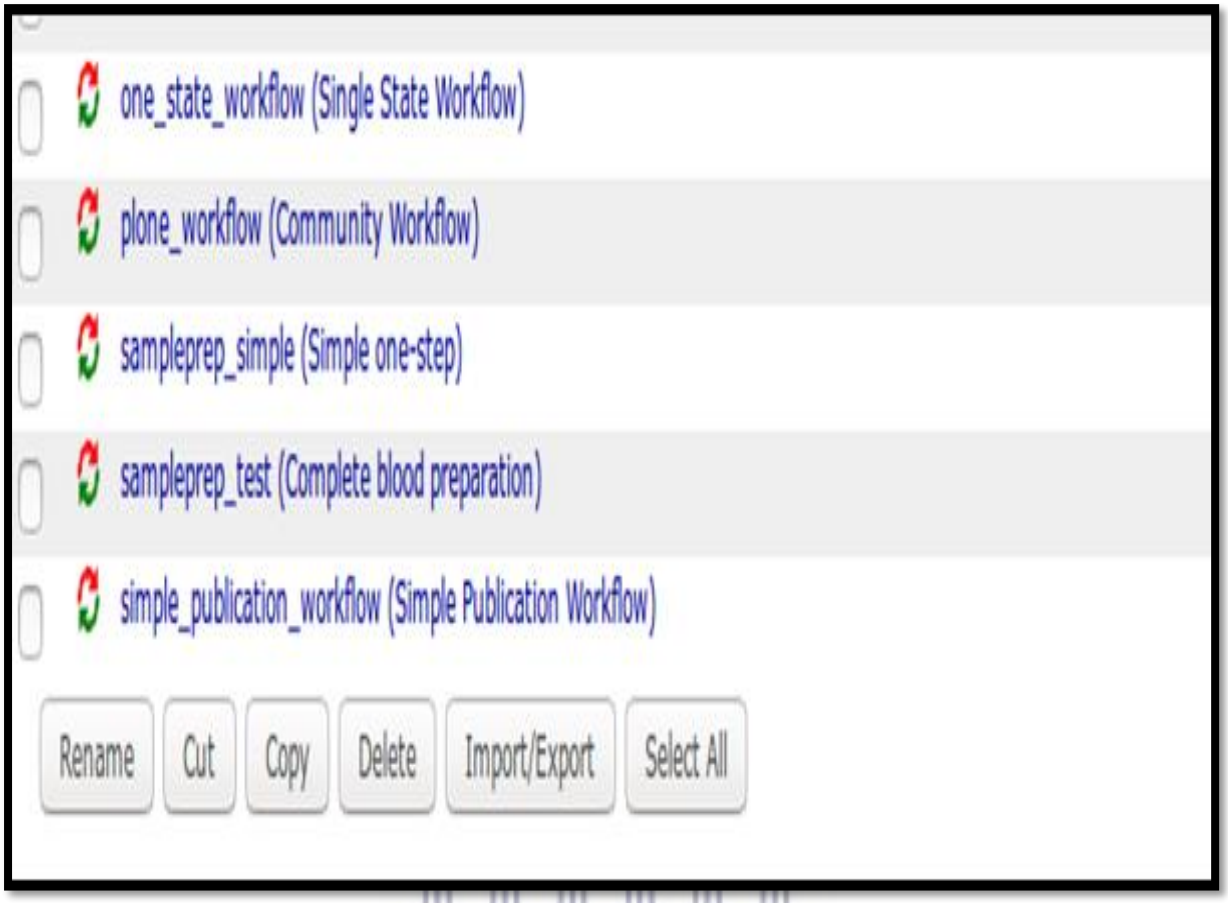


Figure 20: Setting up Plone workflow through the back-end. A unique ID for sample preparation workflow was entered which is preceded with the prefix sampleprep_, followed by the name of the sample workflow option. The workflow tool configured at the back-end for simple one_step and complete blood preparation by clicking on the options created.

A unique ID for sample preparation workflow was entered which is preceded with the prefix sampleprep_, followed by the name of the sample workflow option, title and description is entered for complete blood preparation (Figure 21) and simple one step (Figure 22).

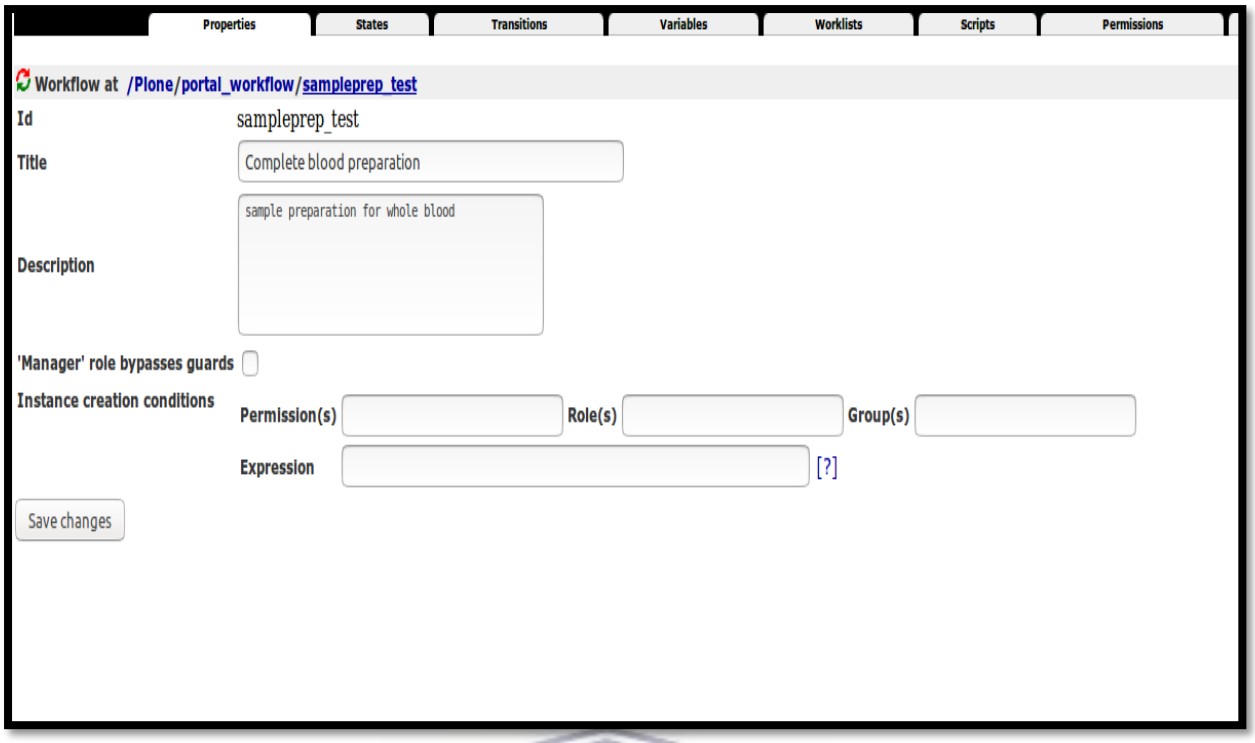


Figure 21: Entering of a title and description of workflow. The description and title of the workflow"complete blood preparation" created for sample preparation options.

The created sample preparation options and setting up the options "simple one step" and complete blood preparation gave access to the options added to default Bika LIMS workflow

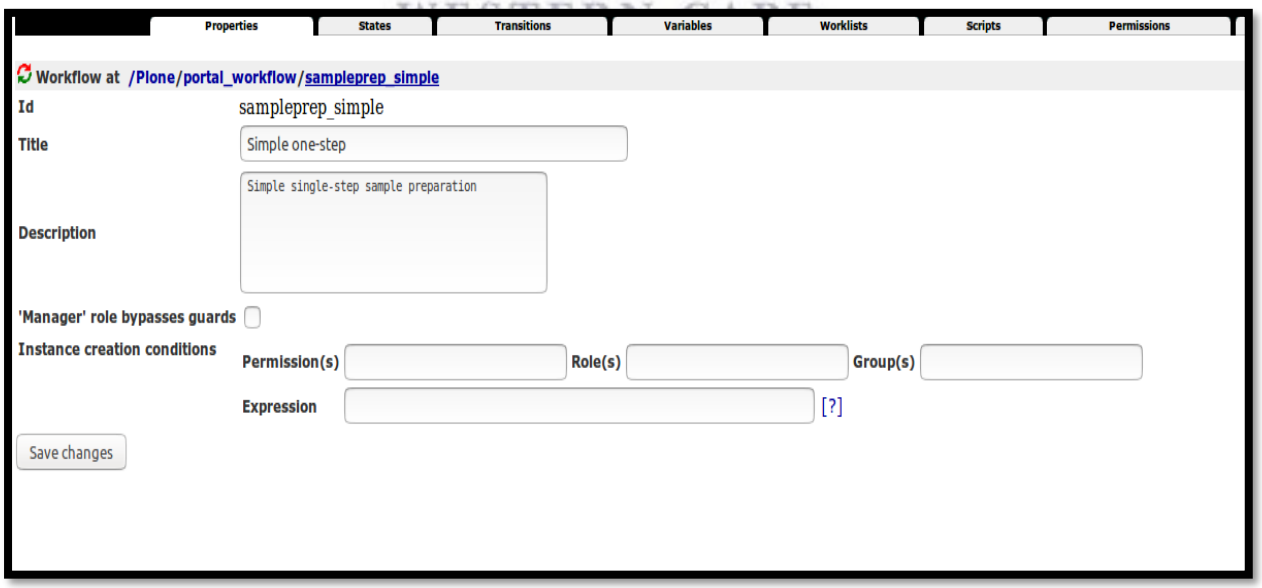


Figure 22: Entering of a title and description of workflow. The description and title of the workflow "Simple one-step" created for sample preparation options.

The IDs of all the states that will be required can be added by clicking the “states tab”. It is important to select the checkbox of the first state, and click set initial state (Figure 23). The steps must be completed properly for it to function correctly.

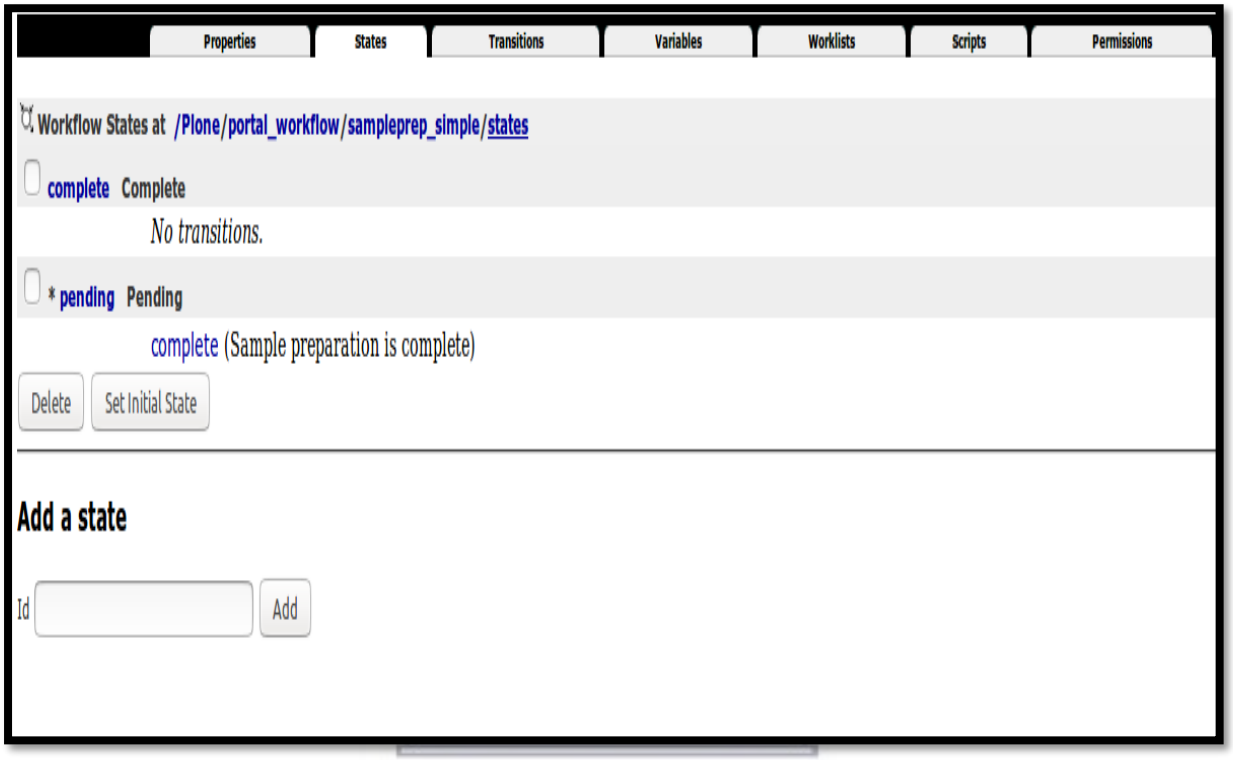


Figure 23: Adding transition to the workflow. Sampleprep_simple_onestep is a single state sample preparation workflow created for managing DNA analysis results.

Transition can be made by clicking on the “transition” tab with simple ID name, and also completing the name formatted field. The final state of the transition ends when there is no more transition. A generalised sample preparation workflow with different sample preparation options was created. The options created specify the sample preparation workflow used in accomplishment of the task in the default Bika LIMS workflow. This will enable different states and transition to be included for diverse preparation sample methods.

3.4 Verification and validation

3.4.1 Verification for workflow accommodating human samples

The steps used in verifying the preparation workflow options field created in the "analysis request" form. This specifies the preparation workflow options used in the default Bika LIMS workflow. Also, the analysis service for human sample that identifies the task requested by the client.

Step 1: All the required fields in the "analysis request" form were completed. An option is chosen from the preparation workflow options "complete blood" or" simple one step" method requested for the preparation. Human sample option was selected.

Step 2: We submitted the form clicking on the submit button requesting for analysis to be done. Here we test for the adaptability of the changes with the system. The request was visible in Bika LIMS.

Step 4: The human sample option chosen for laboratory analysis was visible in instrument import interface for "analysis service" option. After the results were successfully imported, it matched with"Sample ID" and the concentration analyses results in Bika LIMS with file results. Also the "Analysis request" the selected human sample for the preparation workflow to be specify in default Bika LIMS corresponded. The process was repeated multiple times (Appendix D) and (Appendix E).

3.4.2 Verification procedure for the instrument import interfaces

The LIMS depends on data imported into the system for management of samples. Hence, the accuracy of the results data is crucial and must correspond with the generated file results from the instrument used for analysis. The verification method helped input concentration analyses results from BioDrop μLITE and Qubit Fluorometer in appropriate position in Bika LIMS.

Step 1: The results of the analyses were generated from the instrument, retrieved via flash drive through the usb port, and the retrieved analyses results were transferred to a PC via the usb port.

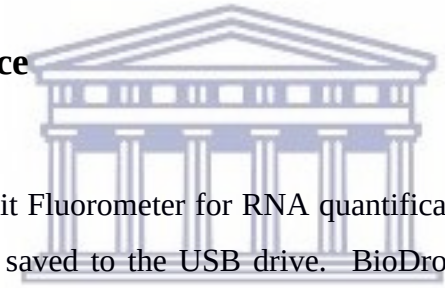
Step 3: The instrument import interfaces for BioDrop μLITE and Qubit Fluorometer was visible in the Bika LIMS instrument import interface. We tested the BioDrop μLITE and Qubit Fluorometer instrument import interfaces by uploading the file and testing with multiple file generated from the instruments analyses. These were done to ascertain if both instruments interfaces appeared in the exact position and could as well upload different file.

Step 4: After every vital field has been completed, analyses results generated were submitted by clicking on the submit button. The submit button could execute the process and the concentration result. We compared the results file concentration column with the results imported into the LIMS and they matched .The required specific result from the analyses results was imported. The test was done several times with multiple generated results (Appendix D) and (Appendix E).

4 Results

In this project, Bika LIMS was successfully installed, and was customised for use in biomedical field to accommodate human samples. Two instruments import interfaces were successfully developed to upload DNA and RNA concentration results from the analyses into the LIMS. The analyses are defined for biospecimens based on the requirements of the project, such as DNA / RNA extraction applied to blood samples, and the resulting quality and purity results of the extracted DNA/ RNA. Results of these analyses are registered and reported to the client. The data are imported into Bika LIMS through an instrument interface and management by the specified sample preparation method physically used for analyses. This is very crucial for integration of additional workflows in the future, for example in analysis of human tissue, urine or plasma proteins.

4.1 Instrument interface



Data was retrieved from Qubit Fluorometer for RNA quantification by selecting the data file and the entire CSV file was saved to the USB drive. BioDrop μLITE was used for DNA quantification and this was connected directly to a computer and results were saved on the pc. All the data generated in both instruments can be opened in any spreadsheet program on a computer. “Analysis Request” form was completed to request for analyses to be carried out, which was customised to include human sample specification for the biomedical field. The client sample ID or client reference fields are used by clients for their own references to the sample; unique from the laboratory ID that was given to each sample after the completion of the request form. The type of sample preparation workflow that was to be used was selected from the dropdown menu (Appendix B). The workflow is currently generic, because of the wide variety of different sample preparation steps, applications and procedures and forms a base on which further functionality can be implemented.

4.1.1 Importing of analyses results from the Qubit Fluorometer

The analyses were carried out using the Qubit Fluorometer instrument. Analyses results data were generated and transferred to USB cable. The instrument import interface for importing of analyses results data from Qubit Fluorometer instrument "life technology Qubit" was selected. The RNA analyses concentration results predefined format corresponding to instrument output results were selected. The type of Analysis Service performed "RNA Extraction" can be selected from the drop down menu to set for import (Figure 24).

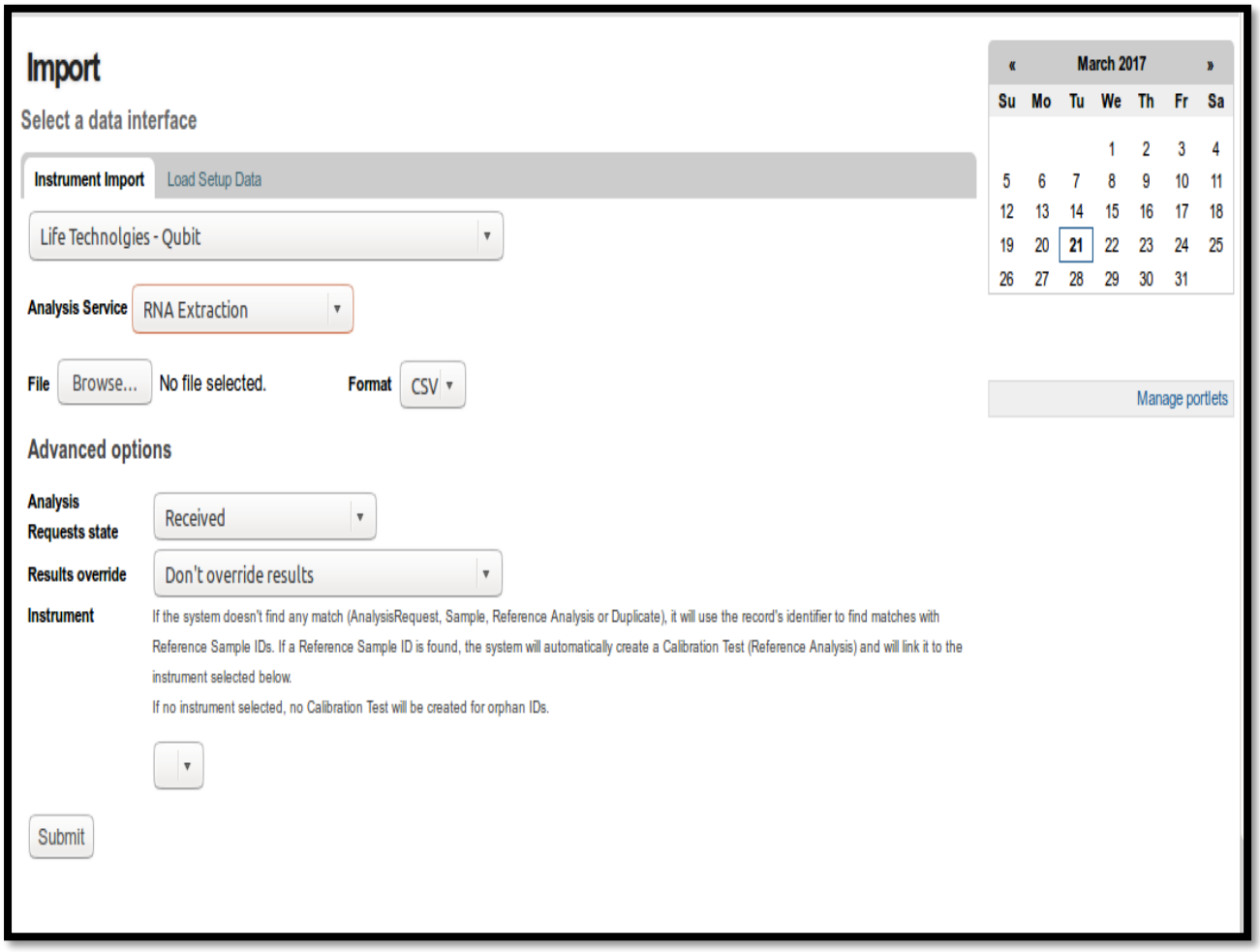


Figure 24: Selection of life technology instrument import interface. The instrument import "Life Technology Qubit" interface option was selected.The type of Analysis Service performed " RNA Extraction" and state in which "Analysis Request" must be captured in Bika LIMS "Received " state was selected to set for import.

The Qubit_01_data.csv file was uploaded and submitted. The RNA concentration results were imported into Bika LIMS by matching the "Clients Sample IDs" in analysis request form and "Sample IDs" in the output of the RNA analysis results "Qubit_01_data.csv" file. Following the analyses requested to be carried out, "Analyses Request" state for each sample moved to "sample due" (Appendix B (I)). The samples were received for sample preparation in the laboratory by clicking on "received" tab to receive the samples (Appendix B (II)). Hence, Bika LIMS automatically generate a unique barcode for each sample when the sample was received (Appendix B (III)) The "Analysis Request State" must be in "received" or "received and to be verified" state to import Qubit_01_data.csv file results into Bika LIMS. The "Analysis Request" state in the import interface "received" state option was selected to correspond with the "Analyses Request" state in Bika LIMS (Appendix B (IV)). The Qubit_01_data.csv file was uploaded, and "result override" options were used to set the rule on overriding existing rejected results. Qubit_01_data.csv concentration results data were parsed into Bika LIMS by clicking on the submit button (Figure 25).

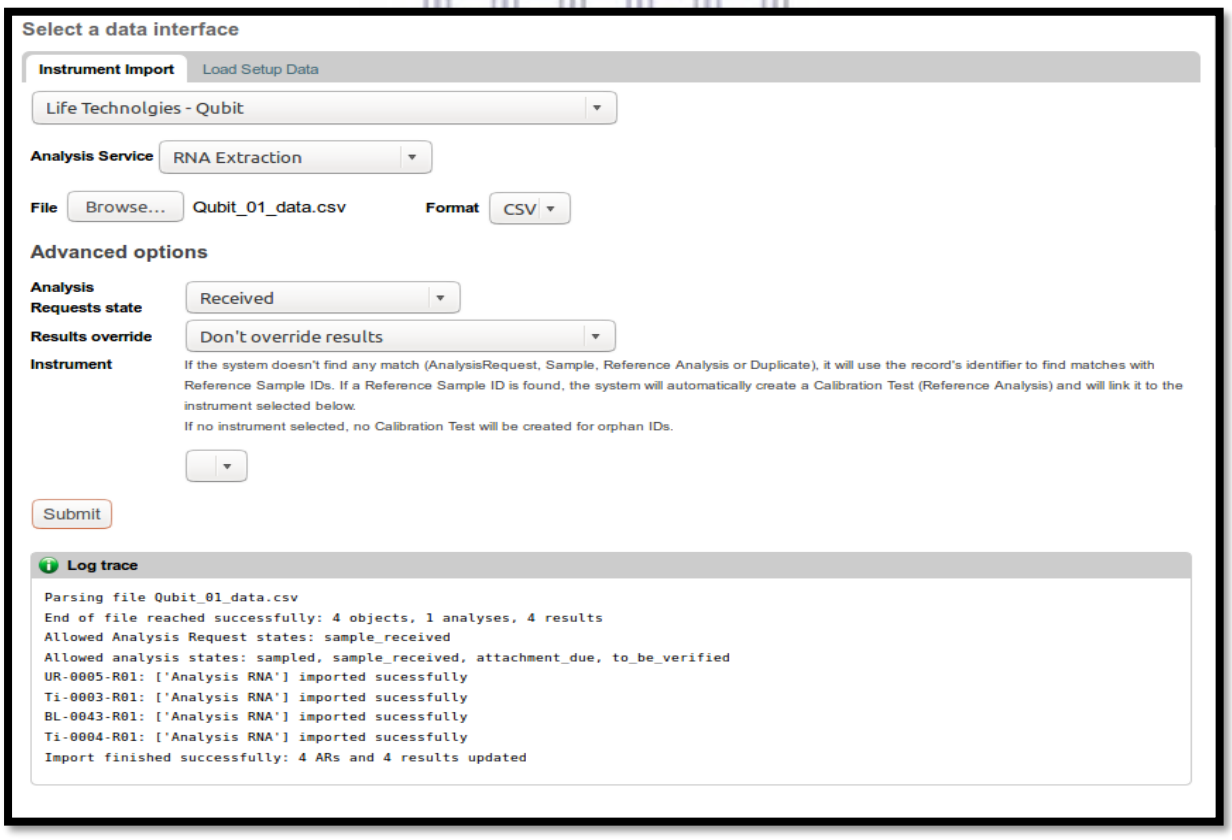


Figure 25: RNA concentration result parsed into Bika LIMS. The concentration from the results analysis from Qubit Fluorometer instrument (Qubit_01_data.csv) file was successfully imported into Bika LIMS

The DNA concentration results were successfully imported into Bika LIMS. (Appendix B (V)). The preparation workflow option "simple one-step" is now linked with its associated information (Appendix B (VI)).

The associated information from the primary workflow is linked with the secondary workflow which is the sample analysis information. The client sample ID "PF0002" and sample type "tissue" prepared using "simple one-step" workflow. The container for specimen separation and the preservation used for preparation was selected in the sample partitions segment. The concentration result for "PF0002" RNA analysis result was "19" (Figure 26).

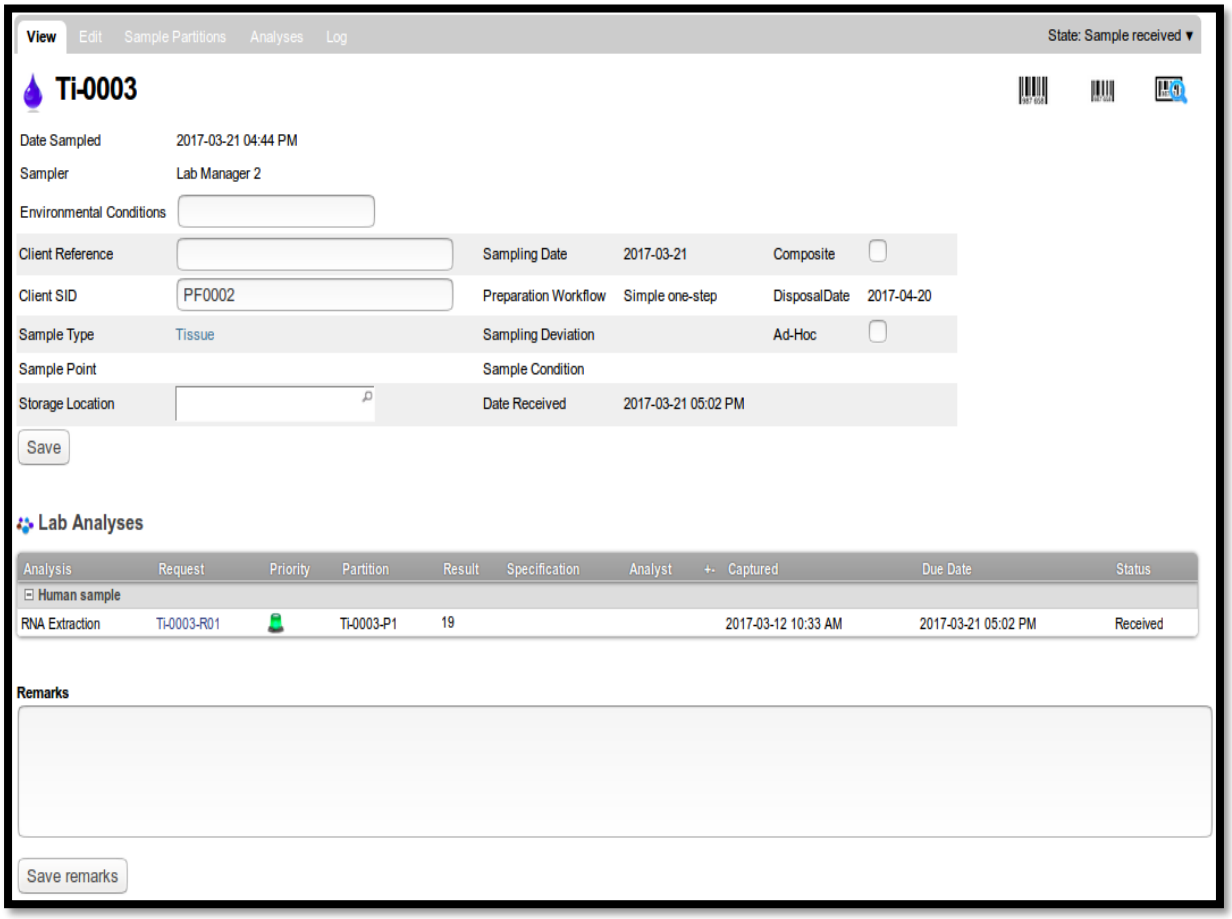


Figure 26: Concentration result from Qubit Fluorometer instrument. Qubit_01_data.csv containing instrument result data was successfully parsed into Bika LIMS. The results are managed by sample preparation option, complete blood preparation workflow.

RNA analyses result imported for client sample ID “PF00002” from Qubit_01_data.csv file was selected for verification (Appendix B (VII)). The result was verified and published after validation by the manager information (Appendix B (VIII)).

4.1.2 Import of analyses result from BioDrop µLITE file

Analysis request form was completed requesting for analysis to be carried out on RNA sample. The samples were received into the laboratory for analysis, the state changes to sample due (Appendix C (I)). Bika LIMS automatically generates a unique barcode for each sample when the sample is received (Appendix C (II)). Analyses request received in the laboratory and barcode generated for each sample (Appendix C (III)). The analyses results data can only be imported into the Bika LIMS, when the analysis requested are in “received” state or “to be verified” state done by navigating to the import page. The format and structure of analysis results of BioDrop µLITE (Figure 11) file differs from Qubit Fluorometer (Figure 16). The instrument interface for importing from BioDrop µLITE was selected from the drop menu (Figure 27).

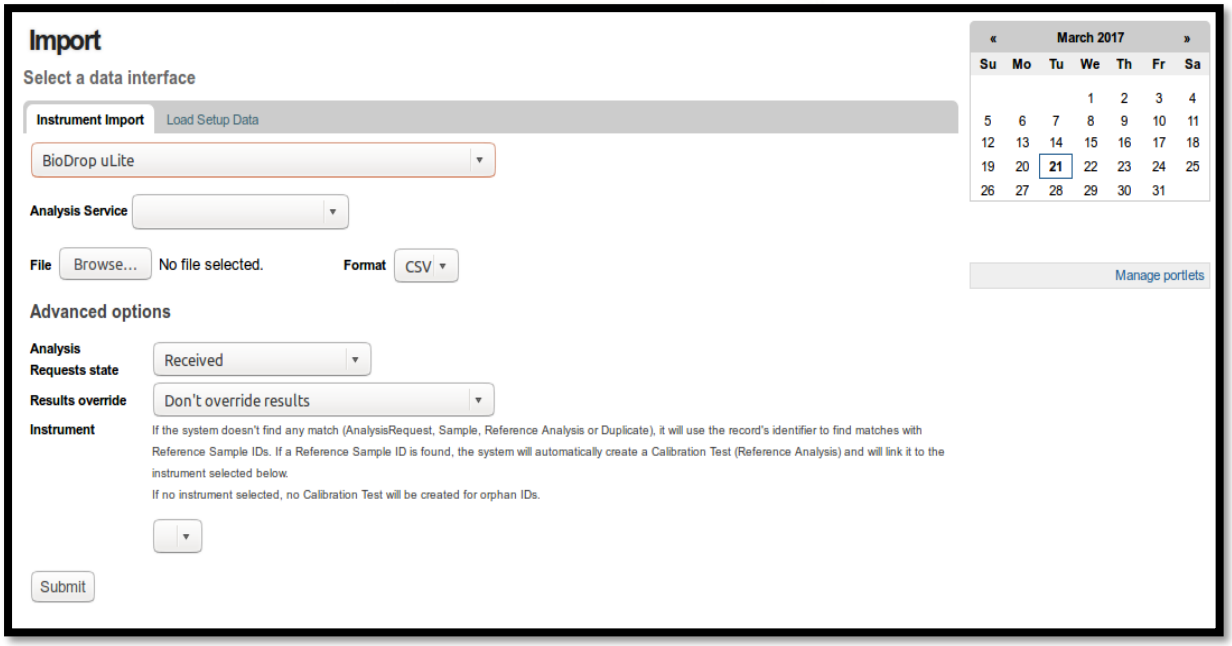


Figure 27: Selection of BioDrop µLITE instrument import interface. The instrument import interface for BioDrop µLITE selected with the BioDrop instrument import interface, set for import after physically receiving sample into BikaLIMS.

Analysis service performed on samples “DNA Extraction” was selected (Appendix C (IV)), BioDrop µLITE file “BioDropuLITE.data.csv” was uploaded and selecting the analysis request “received” state in Bika LIMS before submission for importation (Appendix C (V)). BioDrop µLITE “BioDropuLITE.data.csv” concentration results data successfully imported into Bika LIMS, using unique barcode for identification (Figure 28).

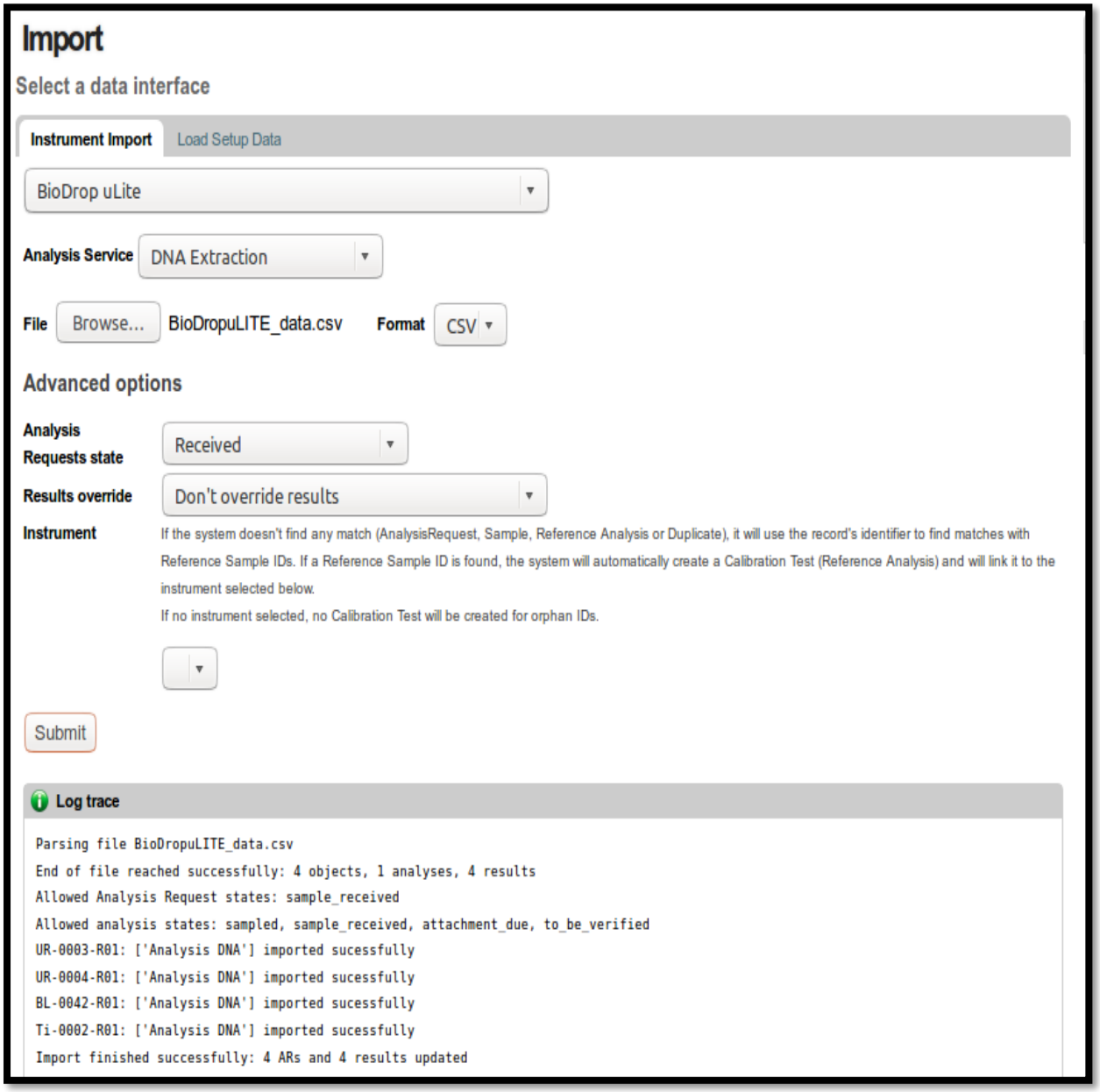


Figure 28: DNA concentration results data successfully imported. BioDropuLITE.data.csv results from the instrument were uploaded from BioDrop µLITE instrument file. The file format was selected and state in which analysis request was captured before submission. BioDrop µLITE “BioDropuLITE.data.csv” concentration results was submitted and was successfully imported into Bika LIMS.

The associated information from the "Analysis Request" is linked with the Bika LIMS workflow which is the sample analysis information. The client sample ID "S0003" and sample type "whole blood" prepared using by "complete blood preparation" workflow. The container for specimen separation and the preservation used for preparation was selected in the sample partitions segment. The concentration result for "S0003" with barcode "BL-0042-R01" DNA concentration result was "46" (Figure 29).

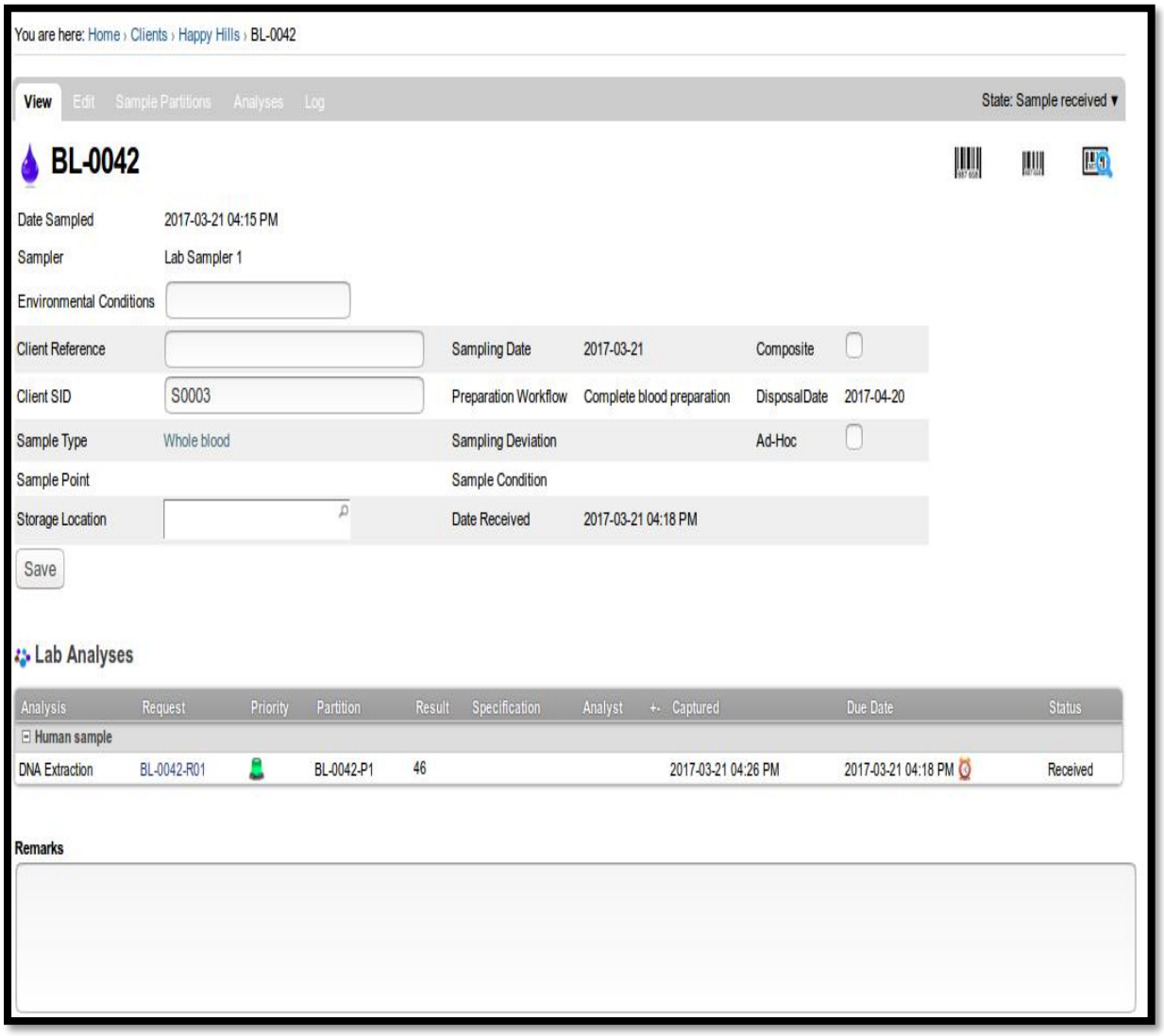


Figure 29: BioDrop µLITE concentration results imported into Bika LIMS. BioDropuLITE.data.csv containing instrument result data was successfully parsed into Bika LIMS. The results are managed by sample preparation option, complete blood preparation workflow.

4.1.3 Sample preparation workflow options

Analysis Request in Bika LIMS has a primary workflow associated with them, and also makes use of secondary workflows. The preparation workflow is dynamically added to the list secondary workflows, and takes control of the states and transition directly after sample is received in the laboratory.

Analysis Request was initially created. The “client sample ID” referencing the patient sample was captured. In the row called “preparation workflow”, a sample workflow option needed for the preparation of each sample was selected from the different options available. Analysis request that was created for DNA sample prior to when the analysis was carried out is displayed below (Figure 30).

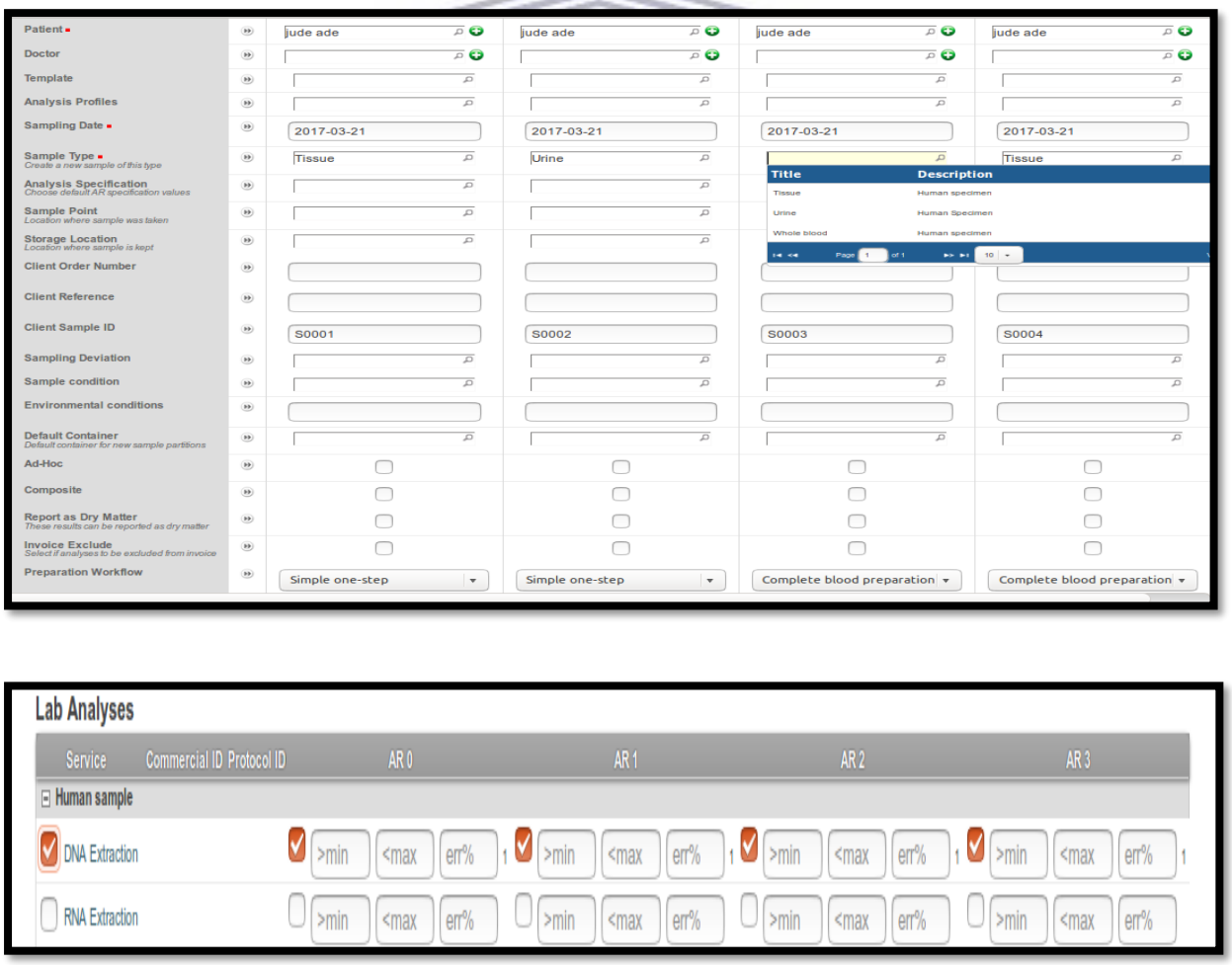


Figure 30: Sample preparation workflow option for each sample.captured. The sample preparation options selected for each sample preparation that will be carried out.

The Analysis Request was submitted and went through the normal Bika LIMS workflow "sample due" state to "received" state transition. Following the submission of the Analysis Request the sample preparation is automatically set to "complete blood preparation" workflow option for client sample ID "S0003" linking the associated information (Figure 31).

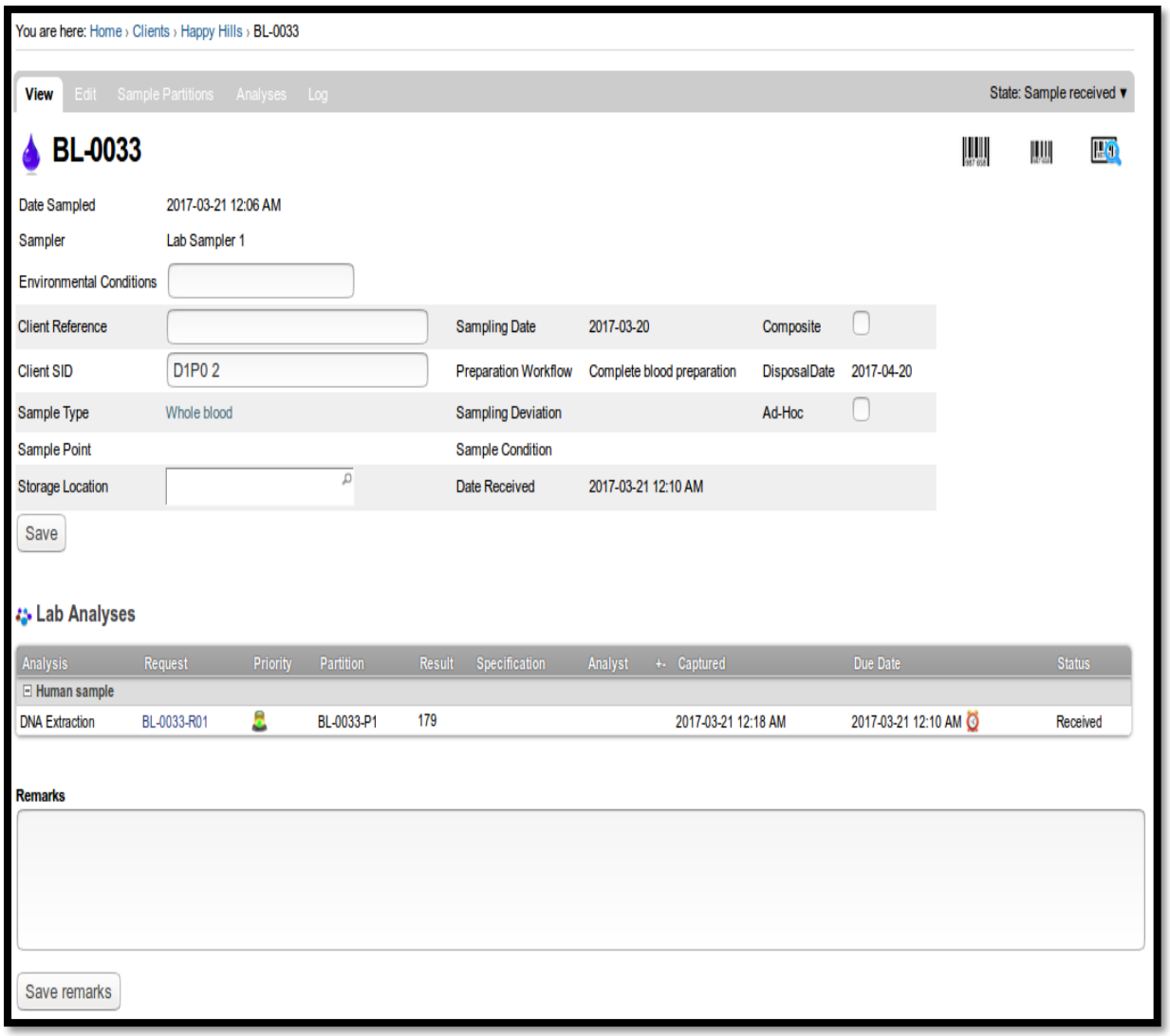


Figure 31: Sample preparation option linking the information. Simple complete blood preparation workflow option linking Client sample ID "S0003" sample information**.**

The result for client sample ID "S0003" imported was linked to the workflow partitioned capturing how the prepared sample was preserved and the container used for preparation in complete blood preparation workflow (Figure 32).

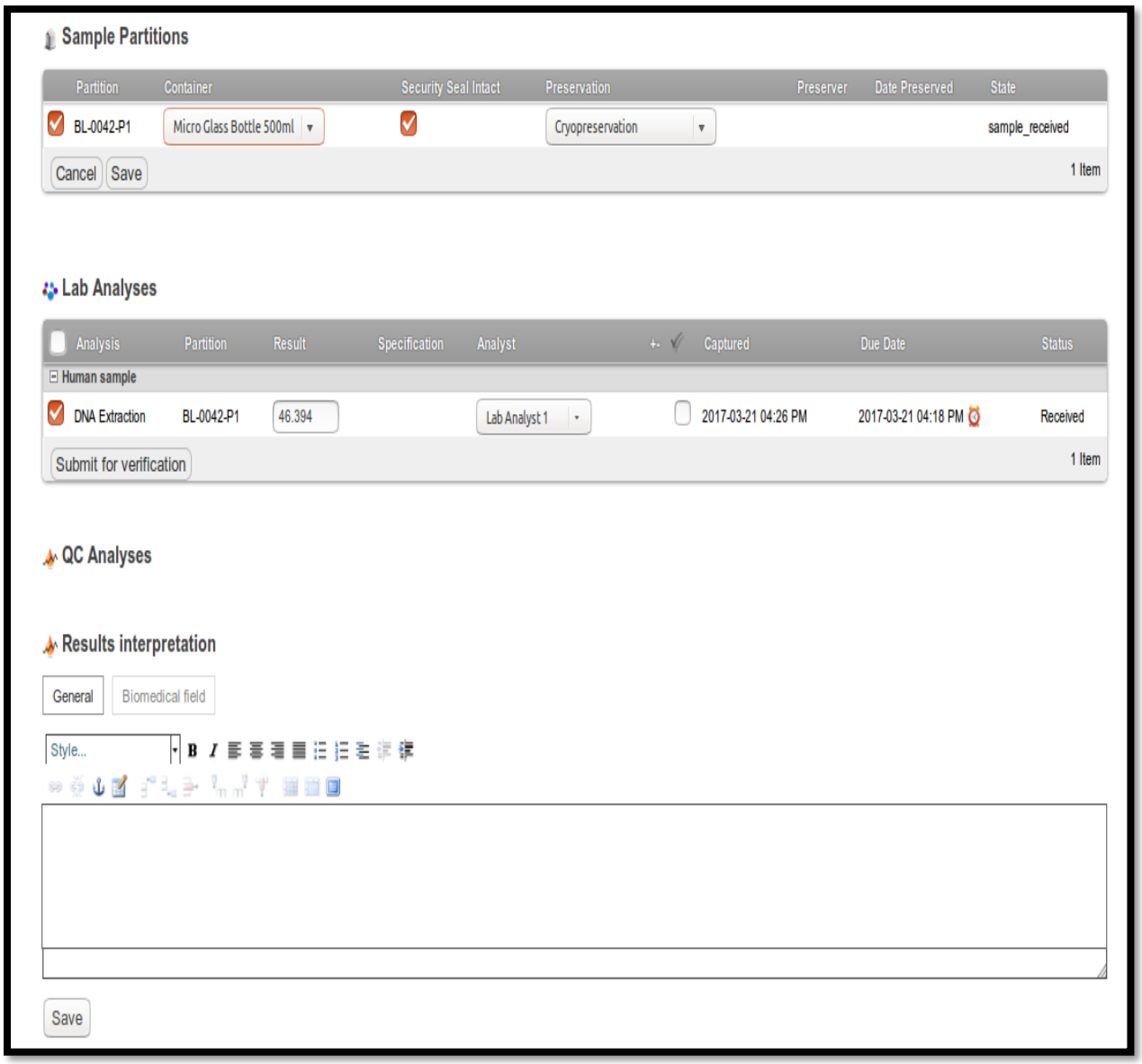


Figure 32: The analyses concentation result in the sample preparation workflow. The DNA analysis result in the sample preparation workflow partitioned, capturing how the prepared sample was preserved and the container used for the samples simple one-step workflow.

The information was verified by the manager and comments could also be added based on the result outcome (Appendix C (VI)). The results could then be published by the manager, if all the results were valid. The published results have the details of the clients on top with the organisation name and sample ID barcode (Appendix C (VII)).

5 Discussion

In this project, an open source LIMS was successfully installed and customised. Bika LIMS is a web-based application designed for use in the laboratory. It has been used in the wine, chemical and environmental laboratories. However, it is yet to be used in biomedical laboratories. The application is modular, and enables modification of the source code to suit a laboratory's specific need. A LIMS system is essential to the effective management of data and the generation of reproducible results. Some available open source or commercial systems may meet the needs of some research fields; however, for those fields the time and monetary cost of a comprehensive commercial system is prohibitive (Grimes, et al., 2014). The core functionality in Bika LIMS was extended through customisation add-on modules and configuration tools that enable the execution of the laboratory workflows. The sample workflow was customised to specify the created sample preparation procedure options used and the development of result import interface to accommodate DNA and RNA signified the ability to customise Bika LIMS to cater for human samples in a biomedical field. The creation of sample preparation workflow options provides a means to manage the DNA concentration results and the various associated information in Bika LIMS workflow. For example, the preparation workflow options "complete blood preparation" and "simple one-step" were added to the "Analyses Request" to indicate the processing performed and the human samples option "DNA Extraction" or "RNA Extraction" to specify the lab analyses tasks and also linked the associated information in Bika LIMS with the option used.

The creation of import interface provides the biomedical laboratories to capture DNA/RNA concentration results generated by BioDrop μLITE and Qubit Fluorometer instruments analyses; normally captured manually, which would improve efficiency and accuracy through the elimination of human transcription errors. Once the data is imported, it limits rechecking of result data for accuracy, then the LIMS can review, validate and QC on the results before sample storage. A user with basic understanding of LIMS will be able use the import interface and manage the result of the concentration in Bika LIMS. The potentials of the LIMS to automate laboratory procedures become crucial as data increases and workflows become more complex, thereby demanding the management of large volume of data (Dubey, et al., 2012).

The import interface was tested by input of data with repetition using various generated CSV result file from BioDrop μLITE (Appendix D) and Qubit Fluorometer (Appendix E). This assures that the system is performing as intended under normal conditions. A workable tested alpha release web- based user import interface is available for use. The ability to import result data will support the automation entry of DNA/RNA concentration analyses by uploading the results through the user import interface directly into Bika LIMS workflow for sample management.

5.1 Implication of study

The open source software will relieve users of administrative work. Hence, they will be able to concentrate on controlling the process on data analysis and paperwork would have been reduced. This is an important consideration for the majority of clinical diagnostics laboratories, where the overwhelming desire to use a single result from analyses results for various selective tests for both RNA and DNA. As a result of this project, laboratory users who use long period of time performing tasks of tedious repetition now have the time to think about the implications of their experimentation and to design effective follow-up projects or develop alternative approaches to their work, which improves their workflow.

Archiving the task of importing the relevant data from the analyses results helps to better understand Zope in supporting TAL, an XML language for instrument form. It also facilitates the use of Plone content management application in sample data management fields.

Bika LIMS functionality combined with the custom modules essential features provide an efficient and intuitive interface to fully manage the results generated from nucleic acid instruments. However, the diverse set of workflows, in situations where this software does not have the essential need, the specifications were used as a prototype. Multiple steps of sample preparation workflow operations from extracted macromolecules such as genomic DNA and concentration metrics can be captured into the system by selecting existing libraries and placing them into separate lanes or partitions (Grimes, et al., 2014). Our method replicates the logic capturing of associated information from the “Analysis Request” linked with the workflow and sample information.

5.2 Limitations of study

. There were issues installing Bika LIMS initially because some dependencies installed were not compatible with Linux, and Bika LIMS did not work with the new version of Plone. The installed dependencies for Linux were upgraded to the latest version and the Plone version compatible with Bika LIMS was installed. However, because of the functionality support provided by old version of Plone, the template form was supposed to handle large amount of data successfully imported through the instrument interface at once. However, it turned out the file system did not scale up very well to handle situations when huge documents have to be managed. The sample preparation steps for every analysis done code breaks when a new version of Bika LIMS was updated. Hence, one step sample preparation options were created to allow the sample management workflow on a page. The module was to identify and extract only the relevant data and format it for importation to LIMS. Creating an instrument import interface for parsing the result is required for each instrument that has a different schema for data, because the data structure was structured in different format based on the instruments used, and not all data generated in analyses results file needed to go to LIMS. Thus,a comprehensive schema that is able to address the characteristics of data from the specific instrument was developed.

5.3 Further research

The use of biomedical instrument import interface is an efficient way to store, easily retrieve and share analytical data in a laboratory.The implementation includes functionality that will support additional workflow, multiple biomedical instruments used in the laboratory for data analysis, with different formats and structures. The LIMS system only accepts CSV and TXT file presently. Also, by adding more template forms to process more analyses requests without complexity will accommodate more analyses at a time. Creating additional file format for other instrument file format in the future would help create a more versatile system.

Further development would be done on providing a workflow to support full clinical samplmanagement procedures of variety of methods. In future, automation of the sample preparation process will be implemented by breaking each step down into a series of operations and time frames and creating several steps of the process that are common to all methods to

consolidate the accessibility and retrievability of experimental data, and also expand the scope of the laboratory management system to other life sciences fields.

6 Conclusion

This project identified two instruments that are key to human biobank and lacking in Bika LIMS, namely BioDrop μLITE and Qubit Fluorometer instruments concentration analyses. The analytical module in Bika LIMS was implemented using PYTHON, by using logic that allows importing of specific analyses parsing result files that were generated by the instrument into the appropriate worksheet, supported the execution of the import interface logic (OpenELIS, 2012). A template was created for the BioDrop μLITE and Qubit Fluorometric instruments used for developing the interface for an analysis import form. The instruments generate results in CSV file format. The LIMS was customised using DCWorkflow to provide fully customisable workflows, Zope to provide a web-based interface, Plone content management framework and Python programming language. A parser was created to read and parse the files uploaded from the import form, by splitting them into parts, extracting the data, and populating key-value pairs. The controller manages the submission of the form by initialising the parser that imports the specific file into the LIMS where it is managed by the customised Bika LIMS workflow. This manages submission of analyses results files into the LIMS, will automatically import the data after upload to avoid transcription error and also provides customised workflow for human sample with a data management solution that promotes data accessibility, increased efficiency and time saving.

Sample preparation workflow option interface was first defined in the LIMS, which was used by sample, analysis request, sample partition and analysis object, enabling the ”sample_prep” to be inserted into an object’s workflow chain. This gave permission to modify the portal content, visible and also linked the associated information in Bika LIMS with the option used. The function will return a list of sample preparation workflows. These were identified by scanning all the workflows IDs for appending of the specified preparation workflow. The tools will allow researchers to rapidly analyse large sample of human specimen of a resource-limited setting to meet the demands of increasing biospecimen collection. This development would create invaluable opportunities for research into prevention, diagnosis, and management of a wide range of important complex diseases with major implications for public health (Soo, et al., 2017). It will also allow researchers to concentrate on the science and less on the manual acquisition of data. In this process the manual operations of Tygerberg medical school laboratory would migrate to the use of Bika LIMS and traditional approaches for data

management would be replaced with a viable system .In this study, it is customised only for the accommodation of DNA and RNA concentration results. Further studies are therefore necessary to add more instruments interfaces use in pathology laboratory and the inclusion of each step sample preparation is being carried out.

Analyses results can now be defined in a suitable format for biospecimens based on the requirements of the project, such as DNA or RNA extraction applied to blood samples, the resulting quality and purity results of the extracted DNA or RNA. Results of these analyses are registered and reported to the client. Bika LIMS, although not specific for human biospecimens, is part of the Bika software ecosystem that includes a Bika Health for healthcare laboratories and Bika Interlab for inter laboratory proficiency testing (Bika, 2016). This will significantly decrease the turnaround time and accuracy of results and ensures data integrity.

7 Bibliography

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8 Appendices

Appendix A: Installing Bika LIMS using Linux operating system.

The latest release of Bika LIMS was downloaded from the Bika organisation site, on the download and install homepage (Smit, 2016). The installation of the software also requires the download of the latest stable Plone (CMS, 2016). The installation was carried out on Linux operating system. However, the process is similar for all systems which Plone supports. Bika LIMS and Plone have some system dependencies that must be installed. Plone is a content management system built on top of Zope, a python-based framework for building a secure web application server with access to the underlying Zope object database (ZODB). These components are written in the Python programming language.

Linux was the operating system used for this project because of its flexibility in adapting to laboratory applications. Plone was installed by downloading Plone 4.3.4. UnifiedInstaller was downloaded after installation of the dependencies (Appendix A). Bika LIMS was added to the buildout file and setup was tested by starting the Zope server. The Zope client helps check for error messages, and makes some modification if there is an error. The server is ready to handle tasks when the message; Zope ready to handle request; is displayed. A new Plone/Bika instance is added by opening the browser and accessing the location "localhost: 8080/manage" in the browser. Once the Plone and Bika instance are added, an admin password is generated by Plone. Copy-paste the password with the user ID and enter, it will navigate to the Zope ZMI, BIKA LIMS option is selected and the form is then submitted by clicking on the submission button.

The process should be similar for all systems on which Plone is supported.

Bika LIMS Linux Installation Steps

1. Plone and Bika LIMS have some system dependencies

   The following list of packages needed to be installed. The package list is valid for Ubuntu 14.04. If you use a different distribution, you may need to find the versions of those packages which are provided with your system.

   sudo apt-get install python-dev build-essential libffi-dev libpcre3-dev gcc
   sudo apt-get install autoconf libtool pkg-config zlib1g-dev git-core libssl-dev
   sudo apt-get install libexpat1-dev libxslt1.1 gnuplot libpcre3 libcairo2
   sudo apt-get install libpango1.0-0 libgdk-pixbuf2.0-0

2. Install Plone

   The latest stable version of the Plone Unified Installer is downloaded.and reading the Plone Installation Documentation.

   A basic command for installing a development environment in Linux to download plone and Python.

   ./install.sh --target=/path/to/Plone --build-python --static-lxml zeo

3. Add Bika LIMS to the buildout.cfg

   Change directory to Plone/zeocluster, and edit buildout.cfg.

   bika.lims and bika health is added to the existing entries beginning with eggs = ,

   eggs =
   Plone
   Pillow
   bika.lims
   Bika.health

   Indentation in buildout.cfg is important, and should be kept uniform for all lines.

   Save the file, and then run bin/buildout again. Buildout will download and install all remaining dependencies.

   If the download is interrupted, simply run bin/buildout again. The process will be resumed.

   Spurious errors may occur while running buildout, and may be safely ignored. Verify successful build from the output of the buildout script, which should include a list of found versions like this:

   ********** **********

Installing Bika-LIMS source

You should already have Plone and Bika LIMS installed. The paths and commands below are for Linux, but following along in windows is simple.

- Download source
- cd Plone/zeocluster/src
- git clone https://github.com/bikalabs/Bika-LIMS.git bika.lims
- Select a git branch
- Edit buildout.cfg
- develop = “ “
- src/bika.lims
- Restart Plone

bin/plonectl restart all

The Bika LIMS distribution in Plone/buildout-cache/eggs/bika.lims* will now be ignored by Plone, and the copy in src/bika.lims is used instead.

If the buildout finishes successfully, an 'adminPassword.txt' will have been created automatically inside the Plone instance folder. It contains the super-user credentials you will need to create the Bika site.

4. Test your setup

   First, start the ZEO Server:

   bin/plonectl zeoserver start

   Then you must start one ZEO Client in the foreground, noting error messages if any and taking corrective action if so:

   bin/plonectl client1 fg

   If you see INFO Zope Ready to handle requests then the server is running. Press Control+C to stop the foreground client.

   To start the Plone server normally, use the following command:

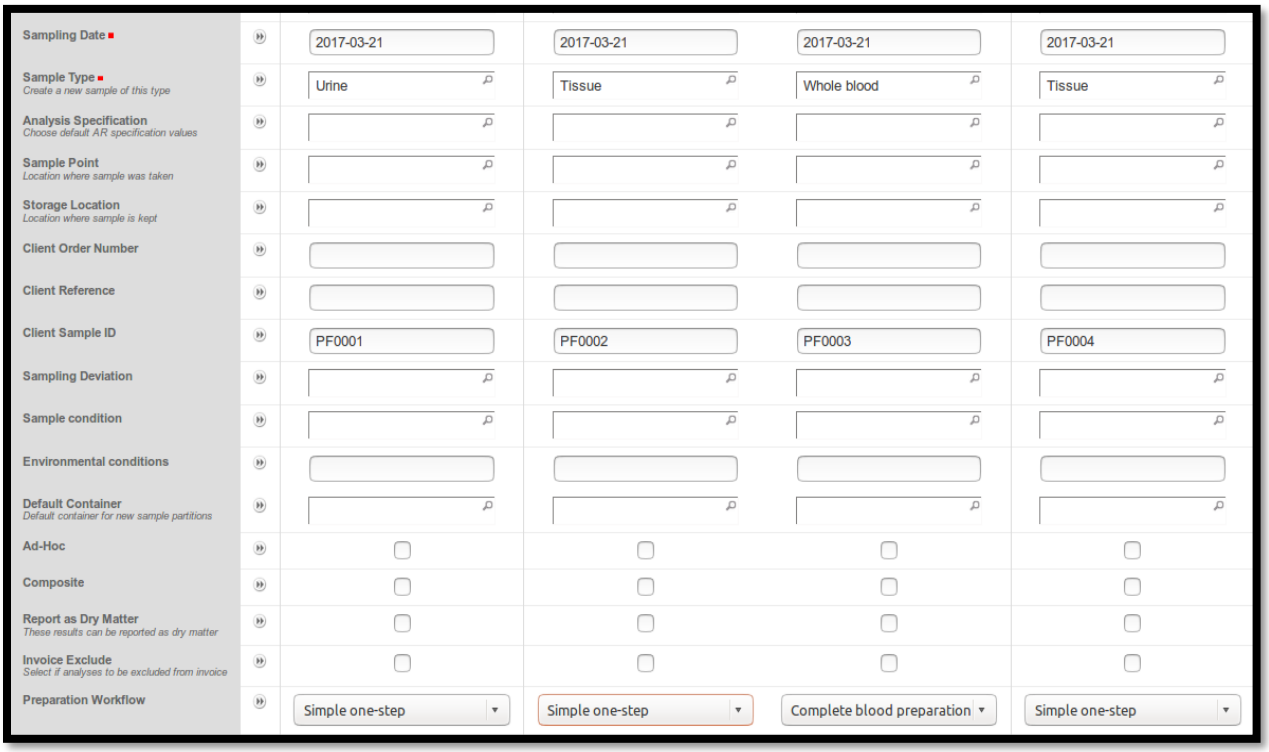
   bin/plonectl start

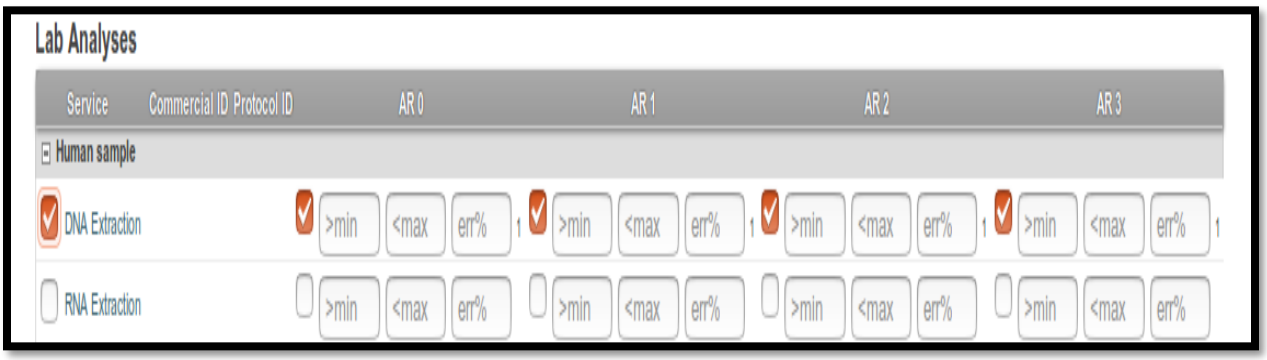
5. Add a new Plone/Bika instance.

   Open a browser and go to http://localhost:8080/. Select "Add Plone Site", and ensure that the Bika LIMS option is checked, then submit the form.

Appendix B: Importation of analysis result from Qubit Fluorometer instrument file and management of sample

I. Completing the relevant fields in the form, clients sample ID, sampling date and sampling typed. Sample preparation option field was created to specify human sample preparation option and selection of the laboratory analysis that is to be carried out.



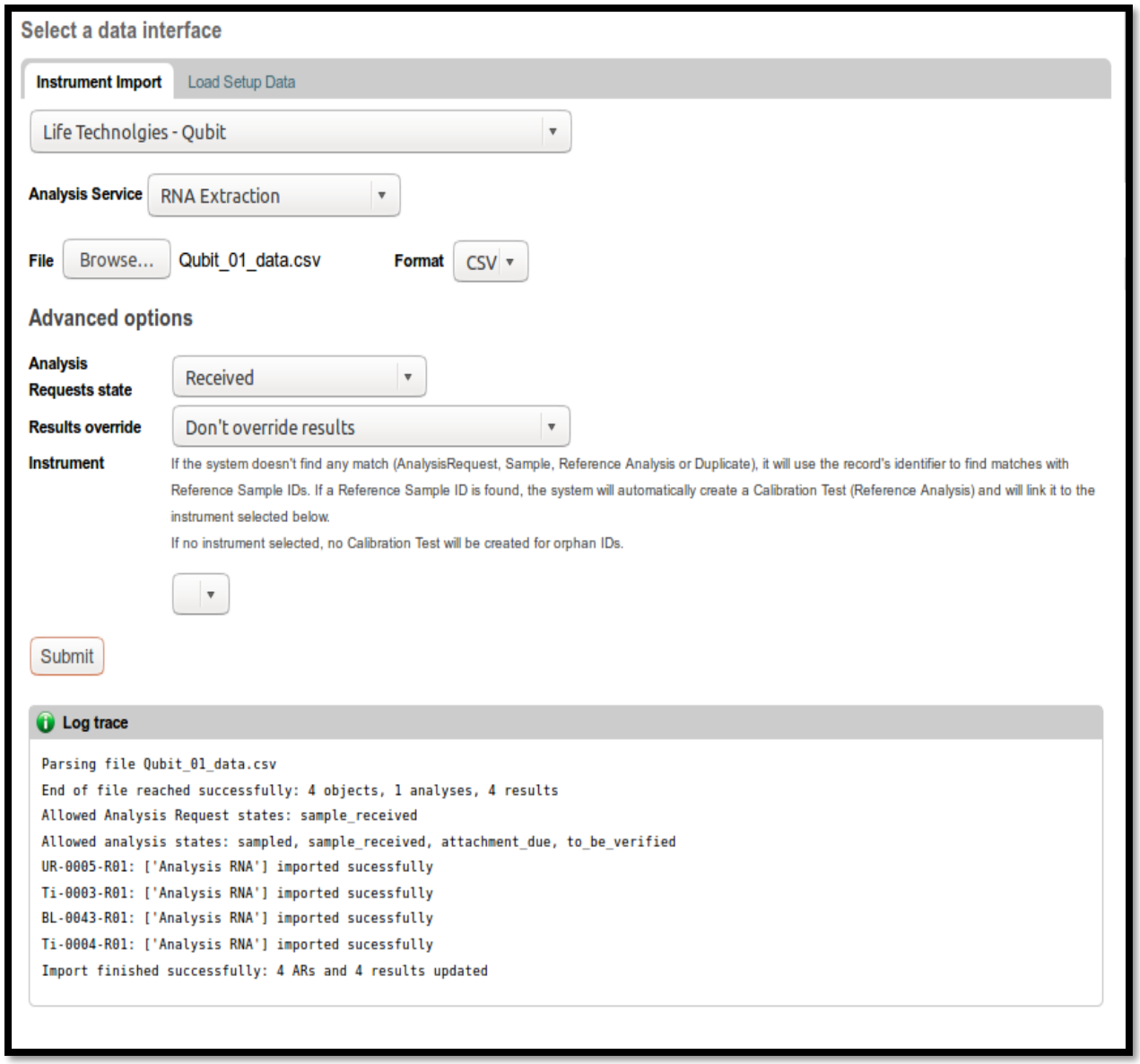


II. Sample analysis request in “sample due” state, waiting to be received in the laboratory

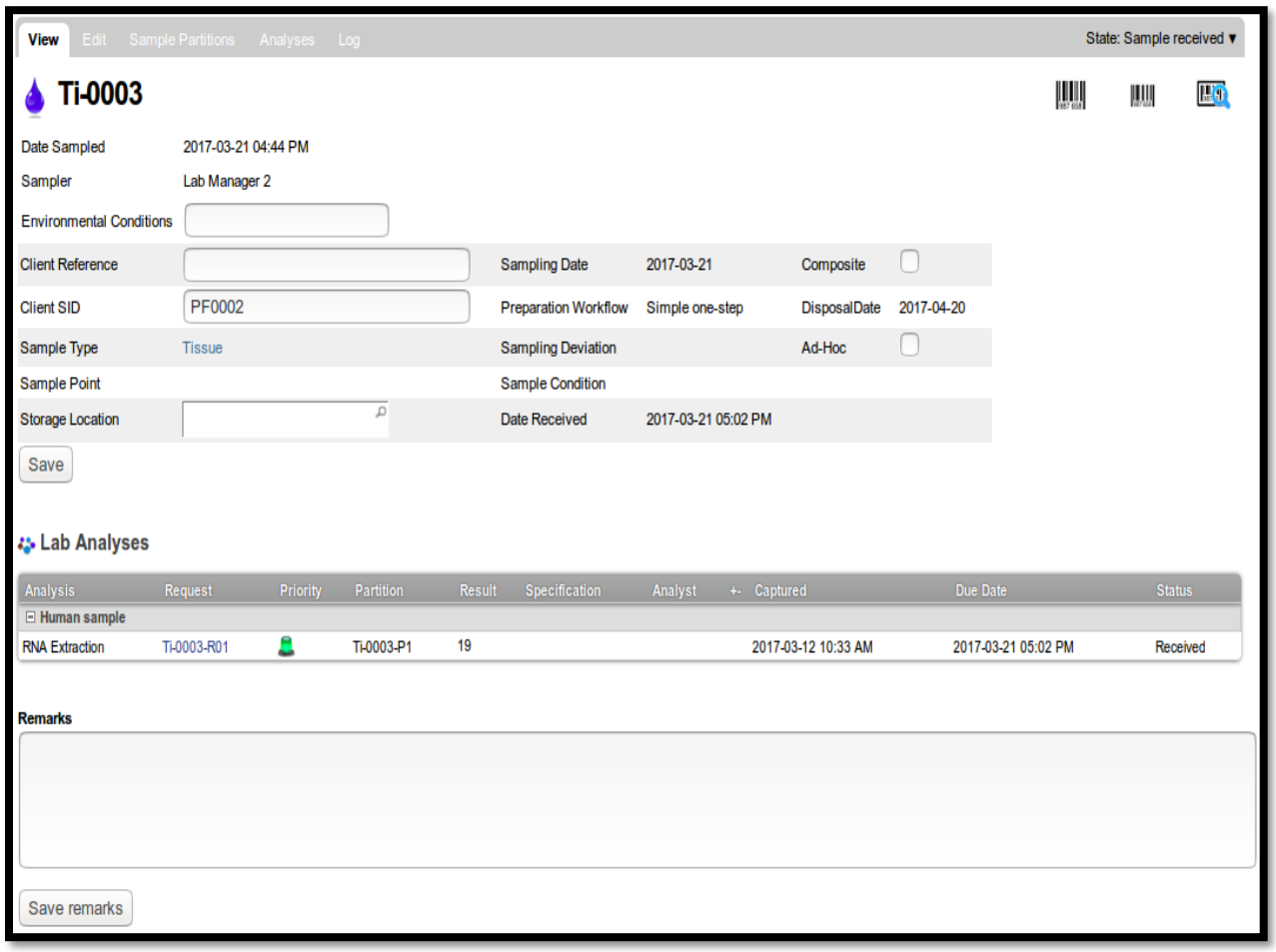
III. Bika LIMS automatically generate a unique barcode for each sample when the sample was received, The printed barcode label was attached to the sample prior going into the laboratory.

IV. The state changes from sample due to received state after sample was received.

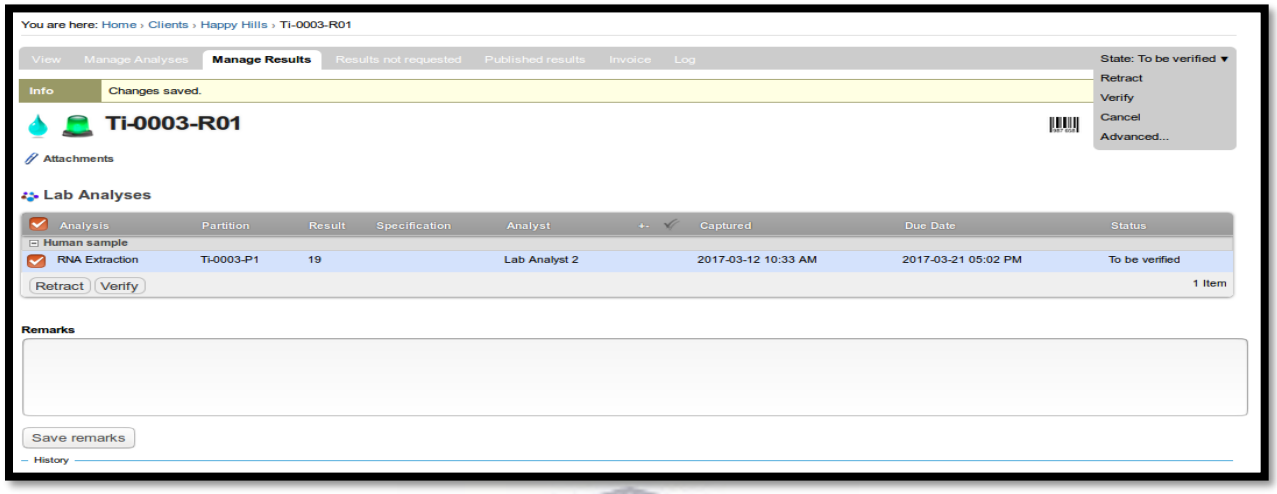
V. Selection of life technology instrument import interface and DNA concentration results was successfully imported into Bika LIMS by submission of results.

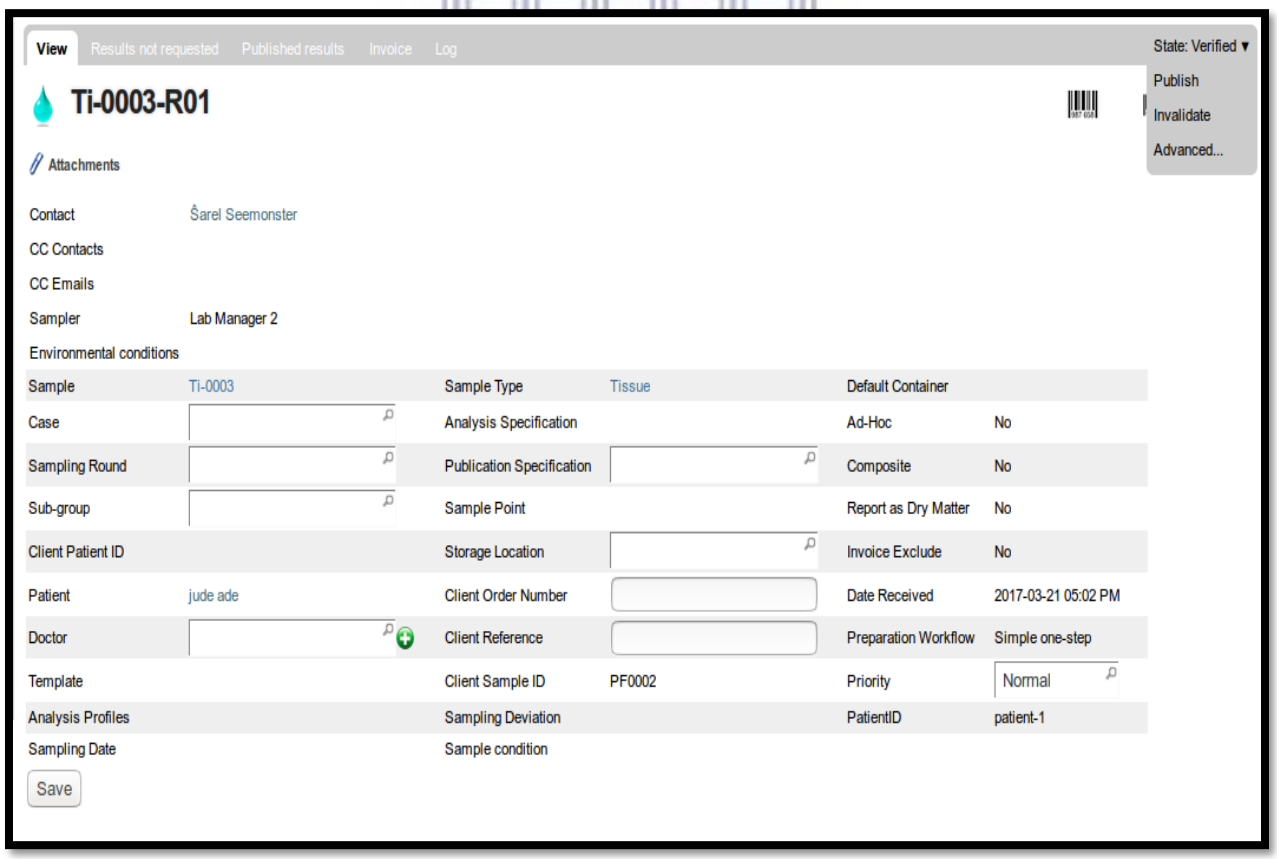


VI. RNA analyses result imported for client sample ID “PF00002” from Qubit_01_data.csv file was selected for verification.

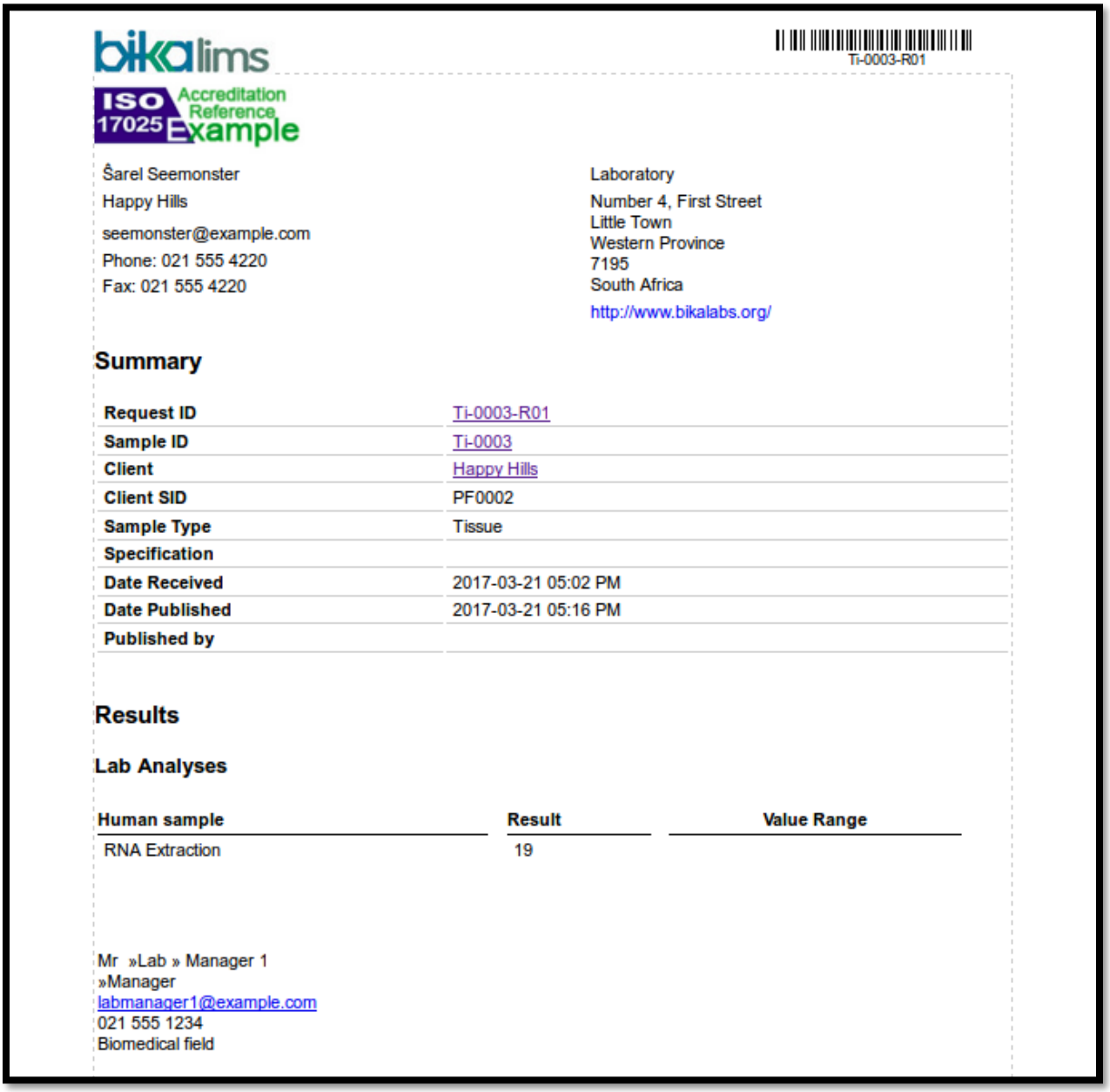


VII. RNA analyses result imported for client sample ID “PF00002” from Qubit_01_data.csv file was selected for verification.





VIII. RNA concentration result for client sample ID “PF0002” was verified and published.



bikalims

Ti-0003-R01

ISO 17025 Accreditation Reference Example

Šarel Seemonster
Happy Hills
seemonster@example.com
Phone: 021 555 4220
Fax: 021 555 4220

Laboratory
Number 4, First Street
Little Town
Western Province
7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	Ti-0003-R01
Sample ID	Ti-0003
Client	Happy Hills
Client SID	PF0002
Sample Type	Tissue
Specification	
Date Received	2017-03-21 05:02 PM
Date Published	2017-03-21 05:16 PM
Published by	

Results

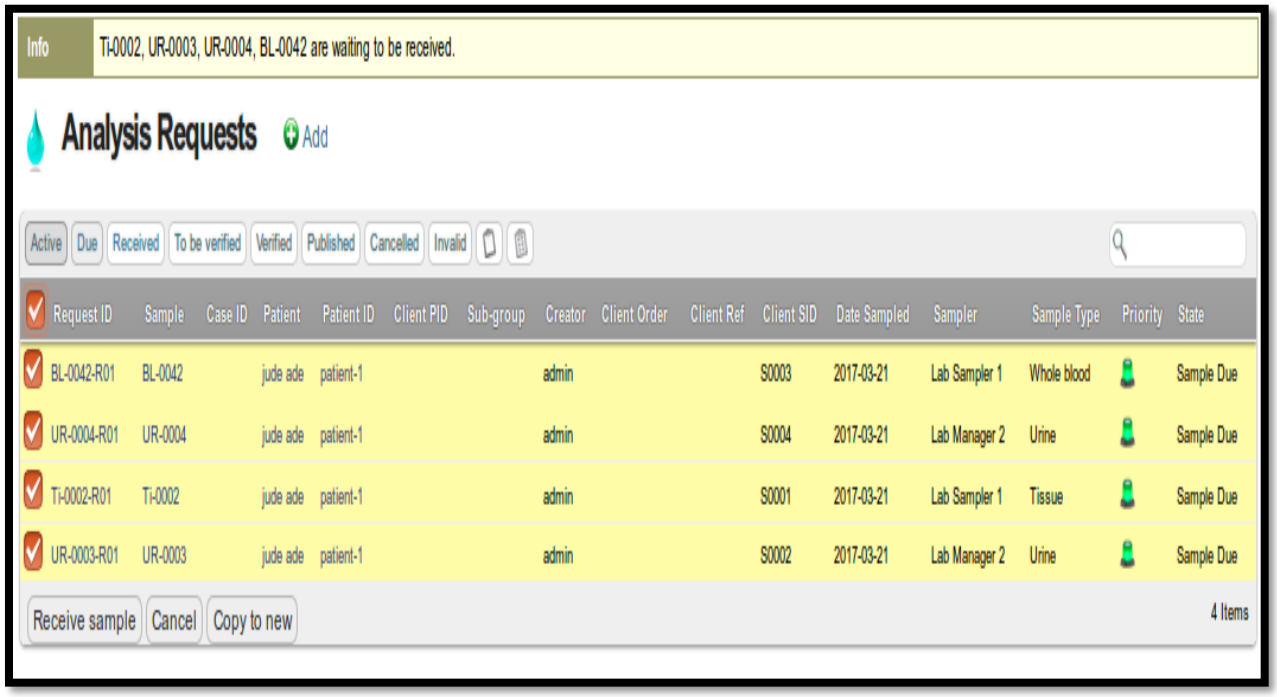
Lab Analyses

Human sample	Result	Value Range
RNA Extraction	19	

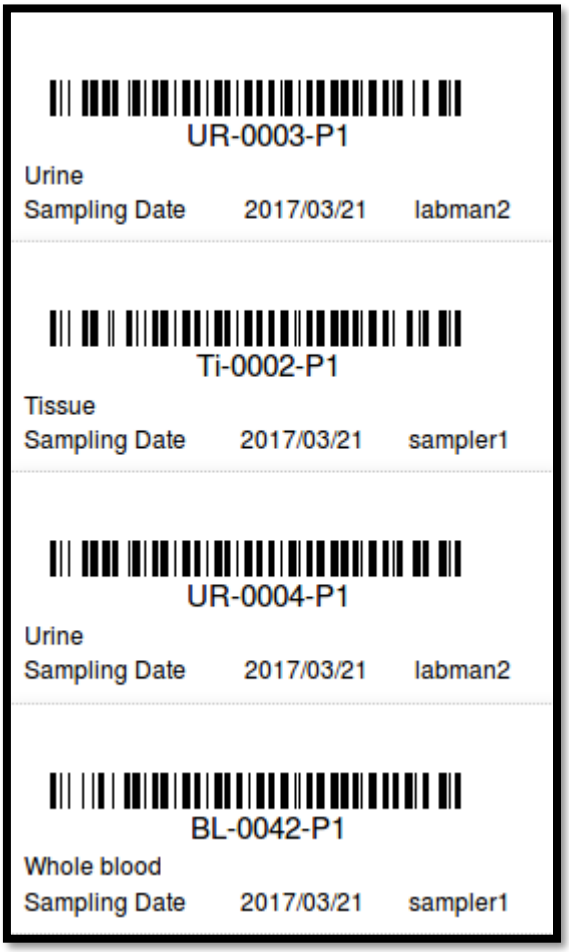
Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

Appendix C: Importation of analysed result from BioDrop µLITE file and management of sample

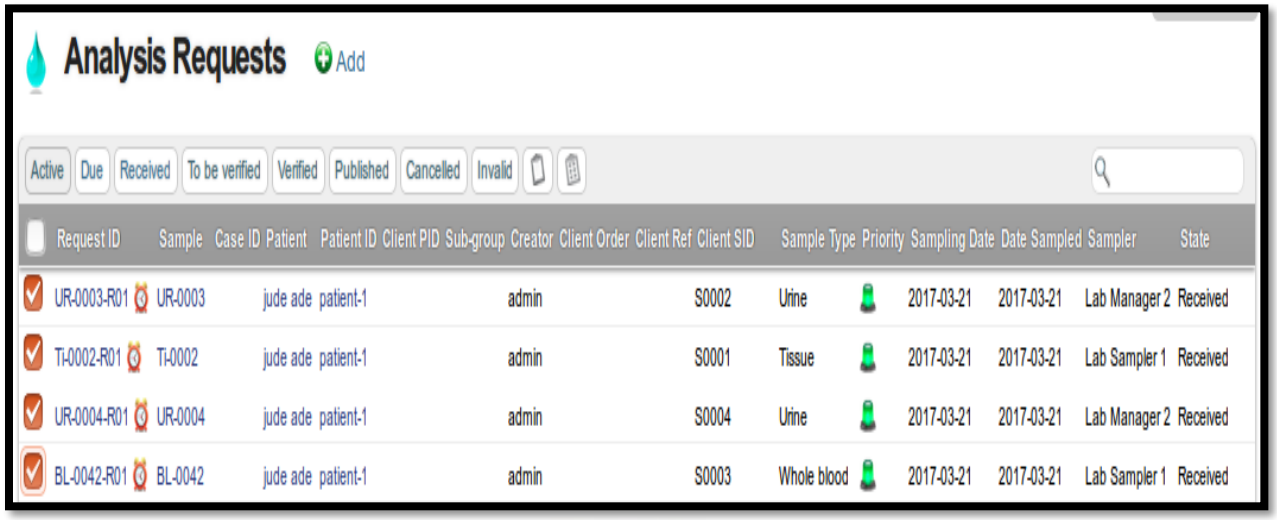
I. The user request for analysis to be carried out the same procedure done for Qubit file, and when the specimen to be sampled is received into the laboratory for analysis, the state changes to sample due.



II. Bika LIMS automatically generate a unique barcode for each sample when the sample was received.

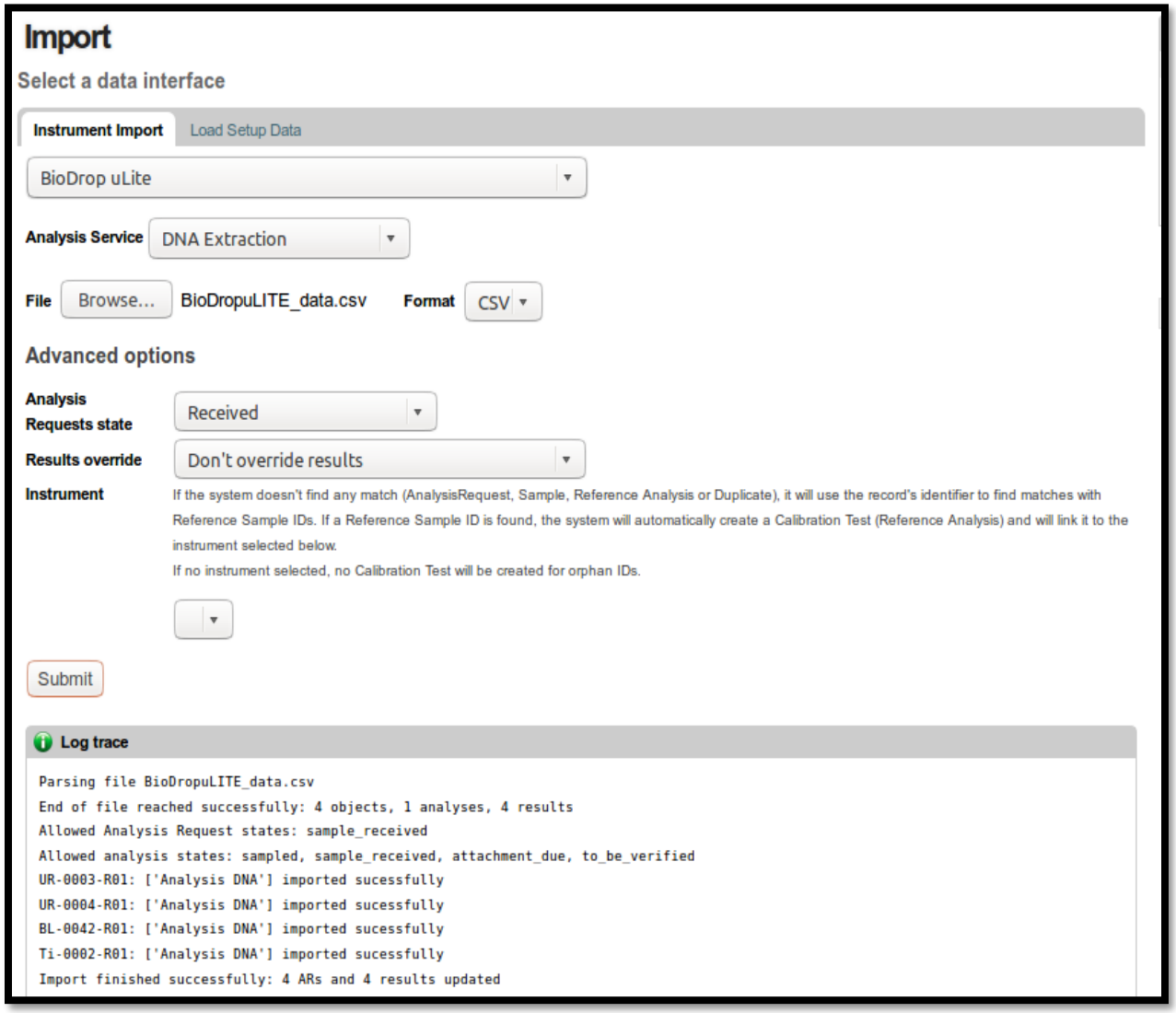


III. Analyses request received in the laboratory and barcode generated for each sample.

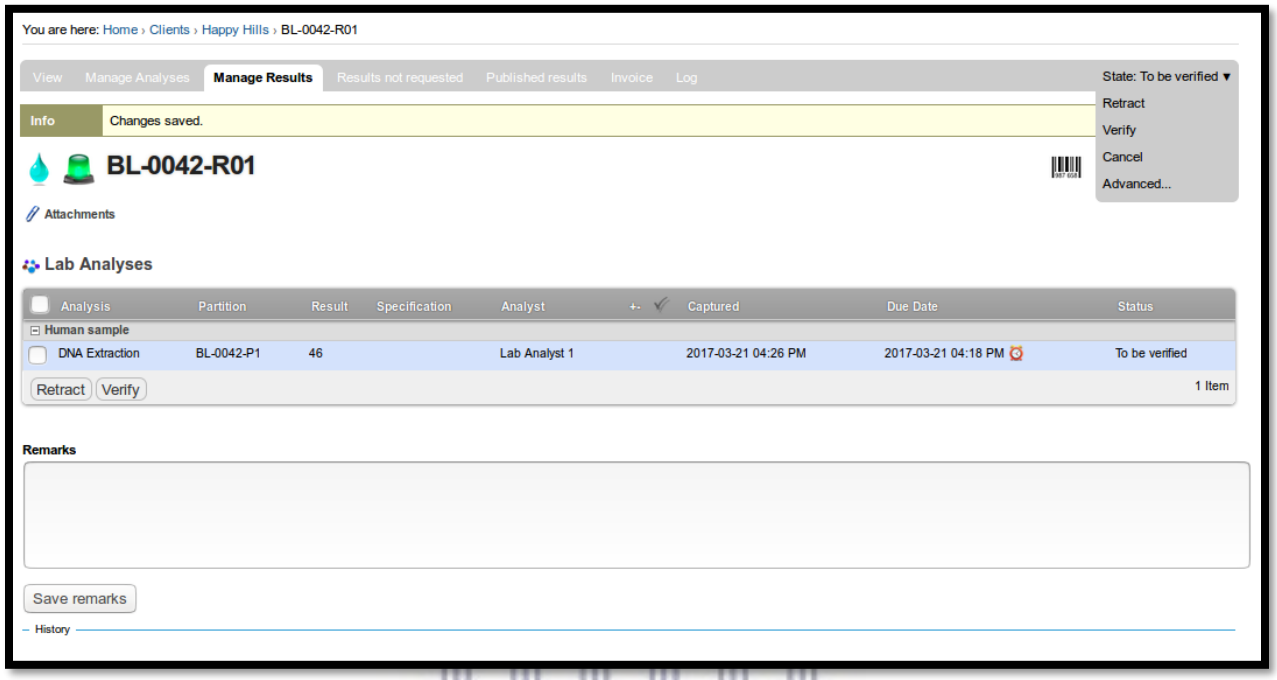


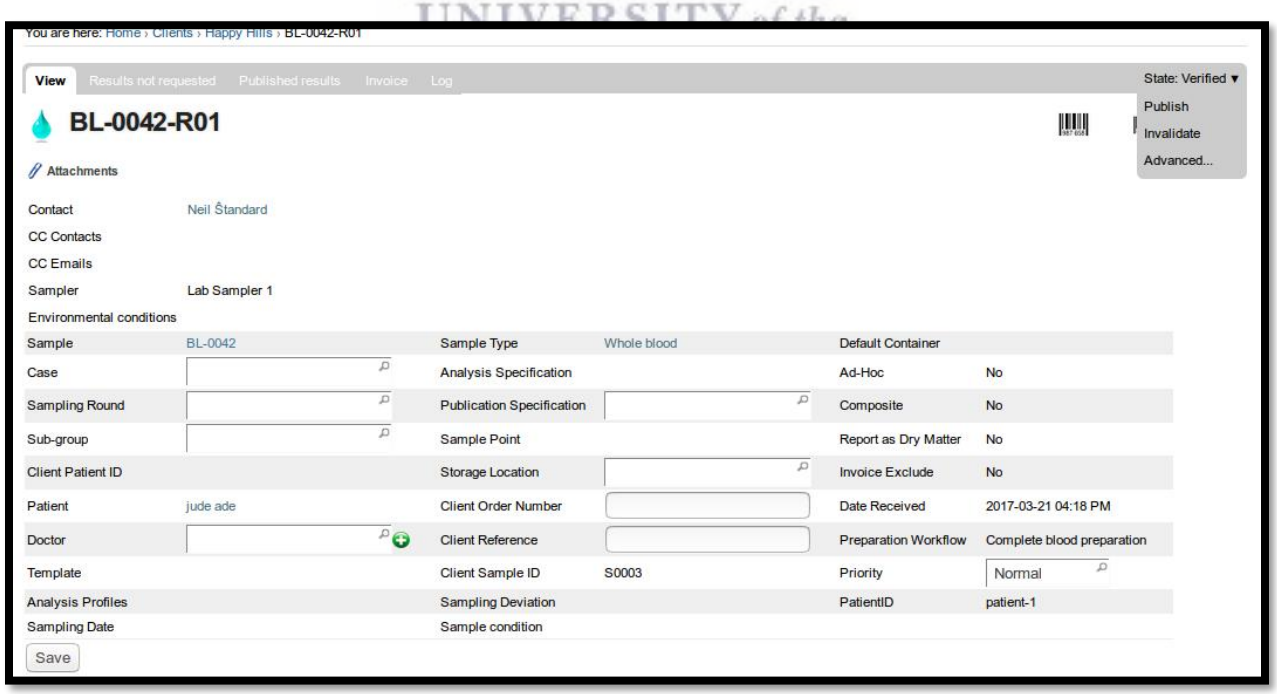
IV. Selection of the BioDrop instrument interface after physically receiving sample into the laboratory.

V. BioDropuLITE_data.csv concentration results imported into Bika LIMS.

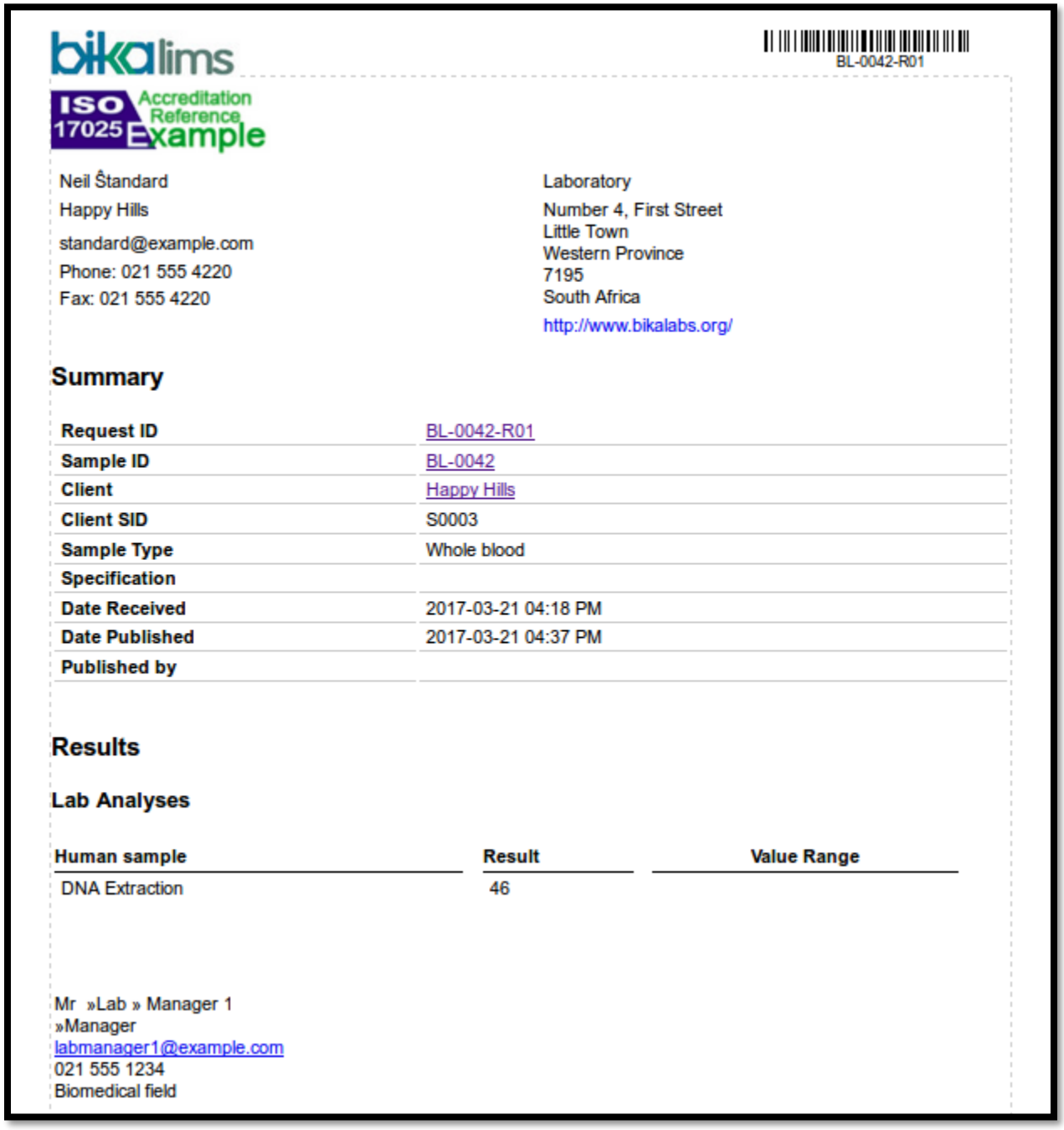


VI. DNA concentration result for client sample ID “S0003” with barcode “BL-0042-R01” and sample information linked with the sample preparation option “complete blood preparation” for result verification.





VII. DNA concentration results for client sample ID “S0003” verified and published



bikalims

BL-0042-R01

ISO 17025 Accreditation Reference Example

Neil Ŝtandard
Happy Hills
standard@example.com
Phone: 021 555 4220
Fax: 021 555 4220

Laboratory
Number 4, First Street
Little Town
Western Province
7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	BL-0042-R01
Sample ID	BL-0042
Client	Happy Hills
Client SID	S0003
Sample Type	Whole blood
Specification	
Date Received	2017-03-21 04:18 PM
Date Published	2017-03-21 04:37 PM
Published by	

Results

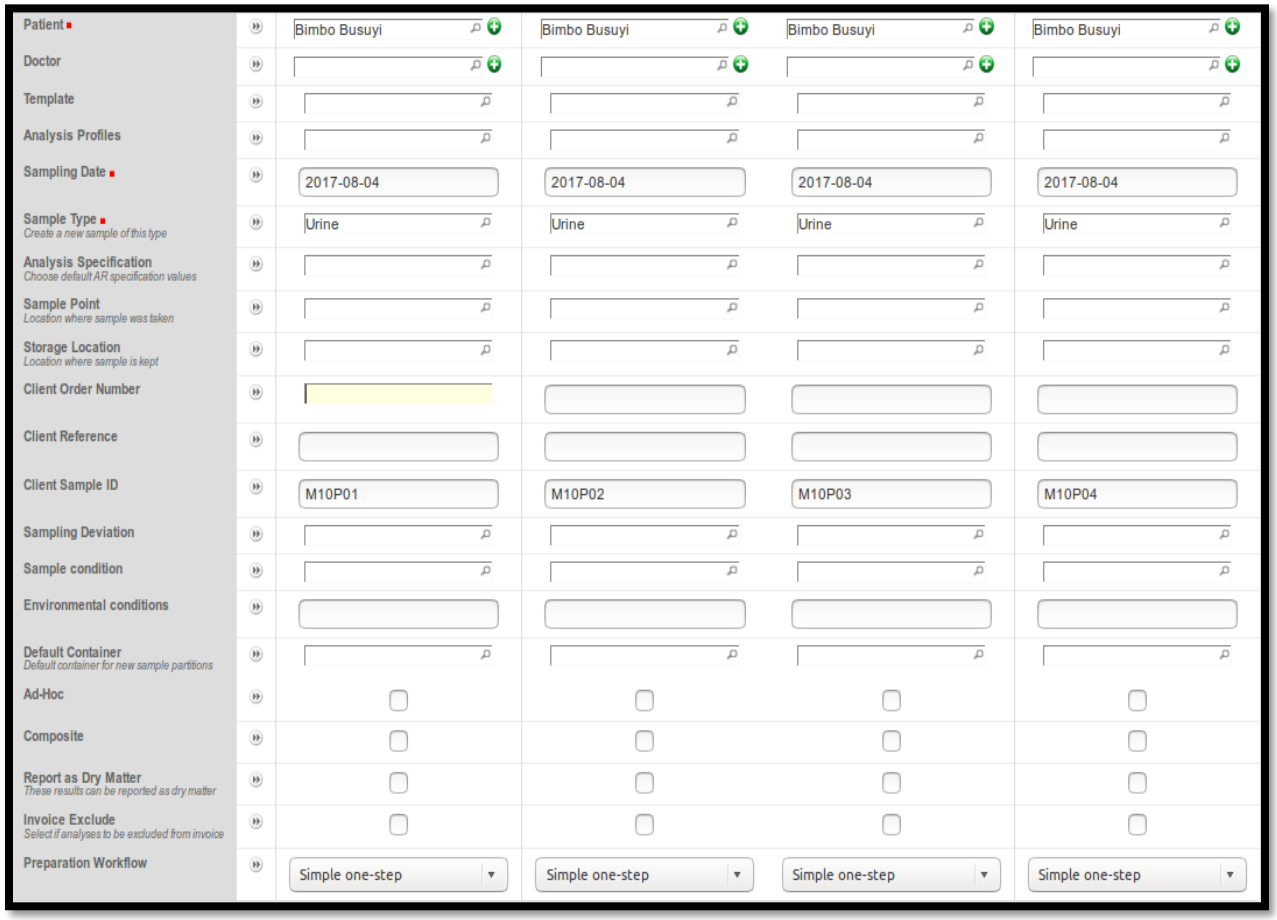
Lab Analyses

Human sample	Result	Value Range
DNA Extraction	46	

Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

Appendix D: Test results for importation of analyses results from BioDrop µLITE instrument file and management of sample

I. Completing the relevant fields in the form, clients sample ID, sampling date and sampling type.Sample preparation option field was created to specify human sample preparation option and selection of the laboratory analysis that is to be carried out.

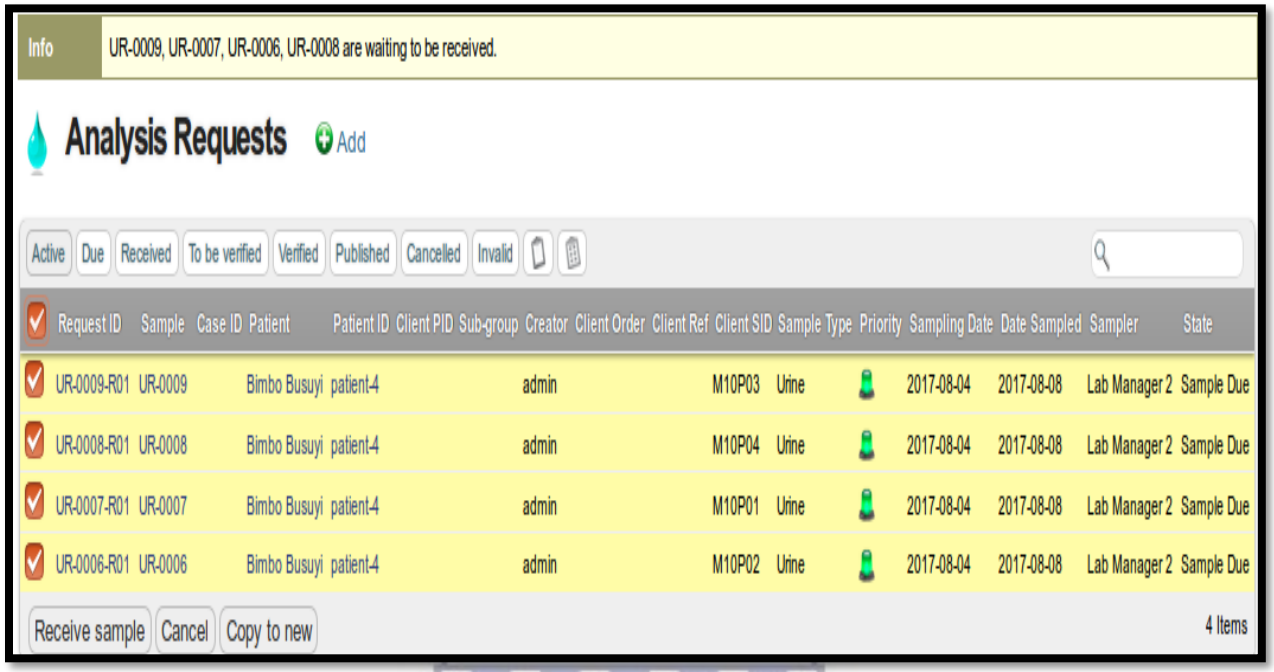


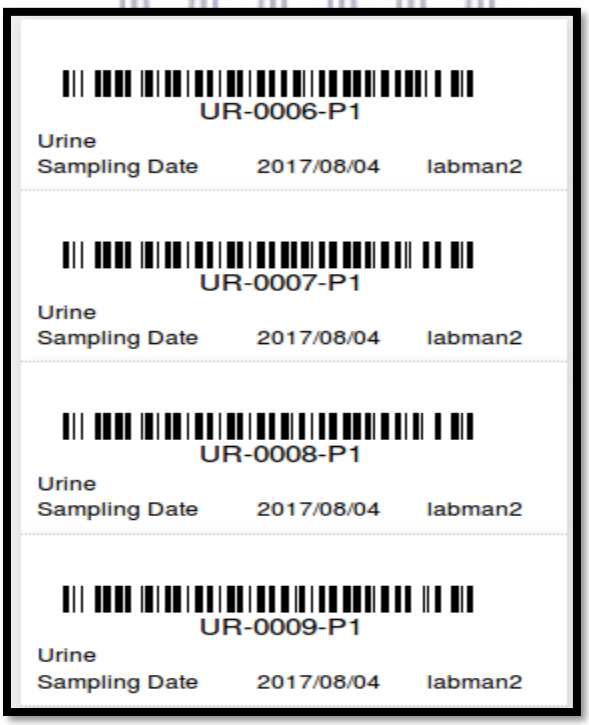
II. Analytical data “BioDropuLITE_data2.csv” generated from BioDrop µLITE instrument.

BioDropuLITE_data2.csv

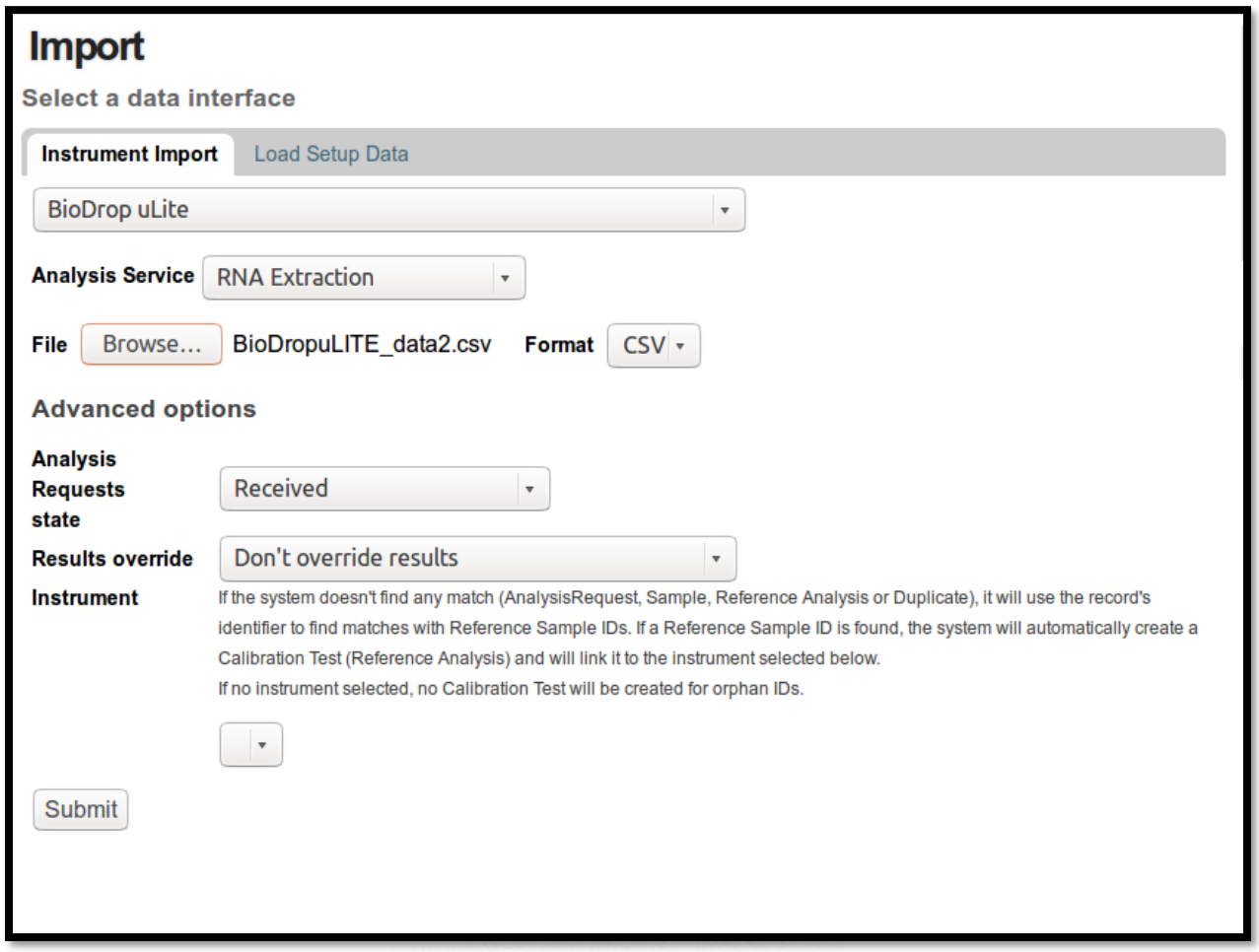
```
Instrument Name,BioDrop µLite,,,,,,,,
Serial Number,1163,,,,,,,,
File Created,04/08/2017,,,,,,,,
Source Application,RNA,,,,,,,,
User,Anon,,,,,,,,
,,,,,,,,,
Pathlength (mm),µLite 0.5mm,,,,,,,,
Bandwidth (nm),1,,,,,,,,
Background,On,,,,,,,,
Dilution Factor,1,,,,,,,,
Integration time (ms),2000,,,,,,,,
Factor,40,,,,,,,,
Units,ng/ul,,,,,,,,
,,,,,,,,,
Date,Time,Sample Name,A230,A260,A280,A320,A260/A230,A260/A280,Concentration
04/08/2017,13:28:00,M10P01,0.024,0.126,0.013,0.003,5.25,1.85,33.457
04/08/2017,13:28:00,M10P02,0.083,0.324,0.123,0.001,3.9,2.63,17.343
04/08/2017,13:28:00,M10P03,0.045,0.084,0.094,0.001,1.87,0.89,88.64
04/08/2017,13:28:00,M10P04,0.053,0.035,0.048,0,0.66,0.729,58.47
```

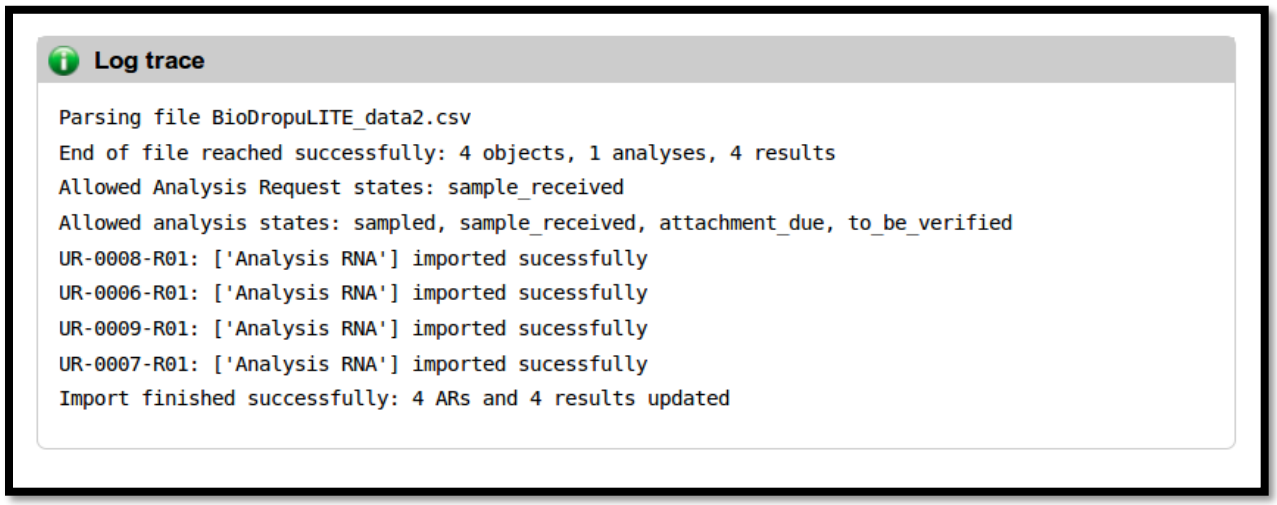
III. Sample received in the laboratory and barcode are generated for the samples.



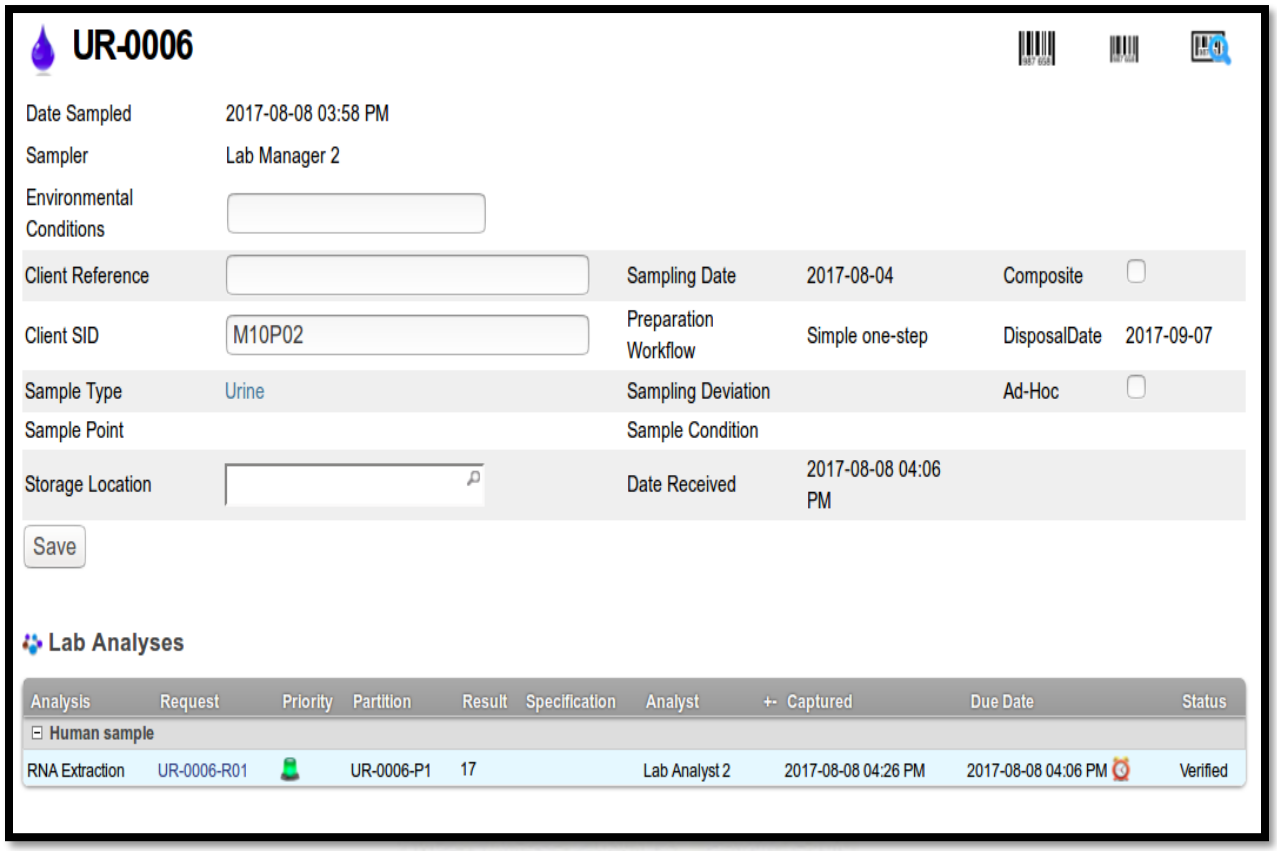


IV. “BioDropuLITE_data.csv” concentration results imported into Bika LIMS.





V. RNA concentration result for client sample ID “MP10P02” with barcode “UR-0006-R01” and sample preparation option “simple one-step” submitted for result verification and verified.



UR-0006

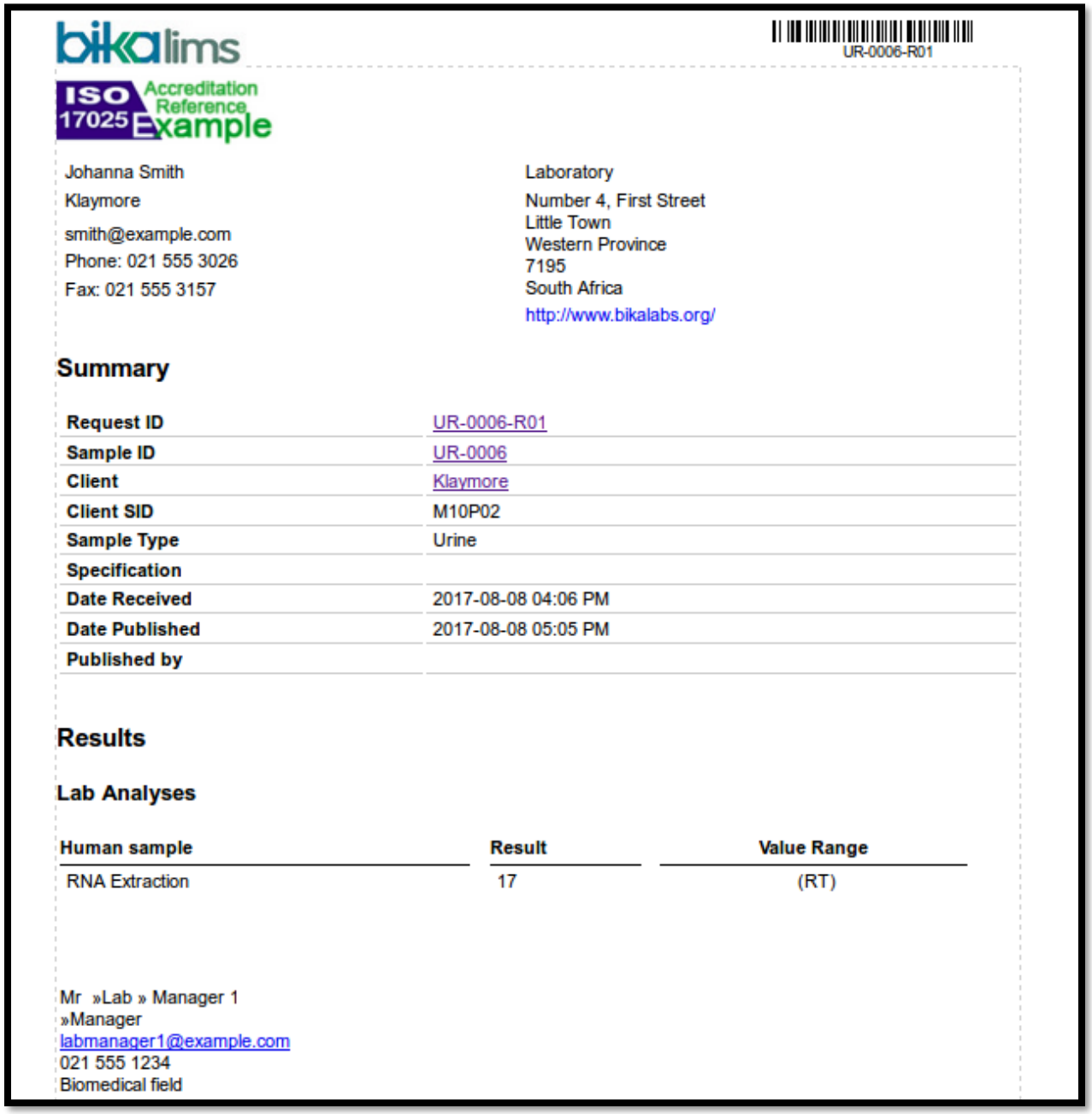
Date Sampled	2017-08-08 03:58 PM				
Sampler	Lab Manager 2				
Environmental Conditions					
Client Reference		Sampling Date	2017-08-04	Composite	☐
Client SID	M10P02	Preparation Workflow	Simple one-step	DisposalDate	2017-09-07
Sample Type	Urine	Sampling Deviation		Ad-Hoc	☐
Sample Point		Sample Condition			
Storage Location		Date Received	2017-08-08 04:06 PM		

Save

Lab Analyses

Analysis	Request	Priority	Partition	Result	Specification	Analyst	+- Captured	Due Date	Status
Human sample									
RNA Extraction	UR-0006-R01		UR-0006-P1	17		Lab Analyst 2	2017-08-08 04:26 PM	2017-08-08 04:06 PM	Verified

VI. RNA concentration result for client ID “M10P02” published.



bikalims

UR-0006-R01

ISO 17025 Accreditation Reference Example

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7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	UR-0006-R01
Sample ID	UR-0006
Client	Klaymore
Client SID	M10P02
Sample Type	Urine
Specification	
Date Received	2017-08-08 04:06 PM
Date Published	2017-08-08 05:05 PM
Published by	

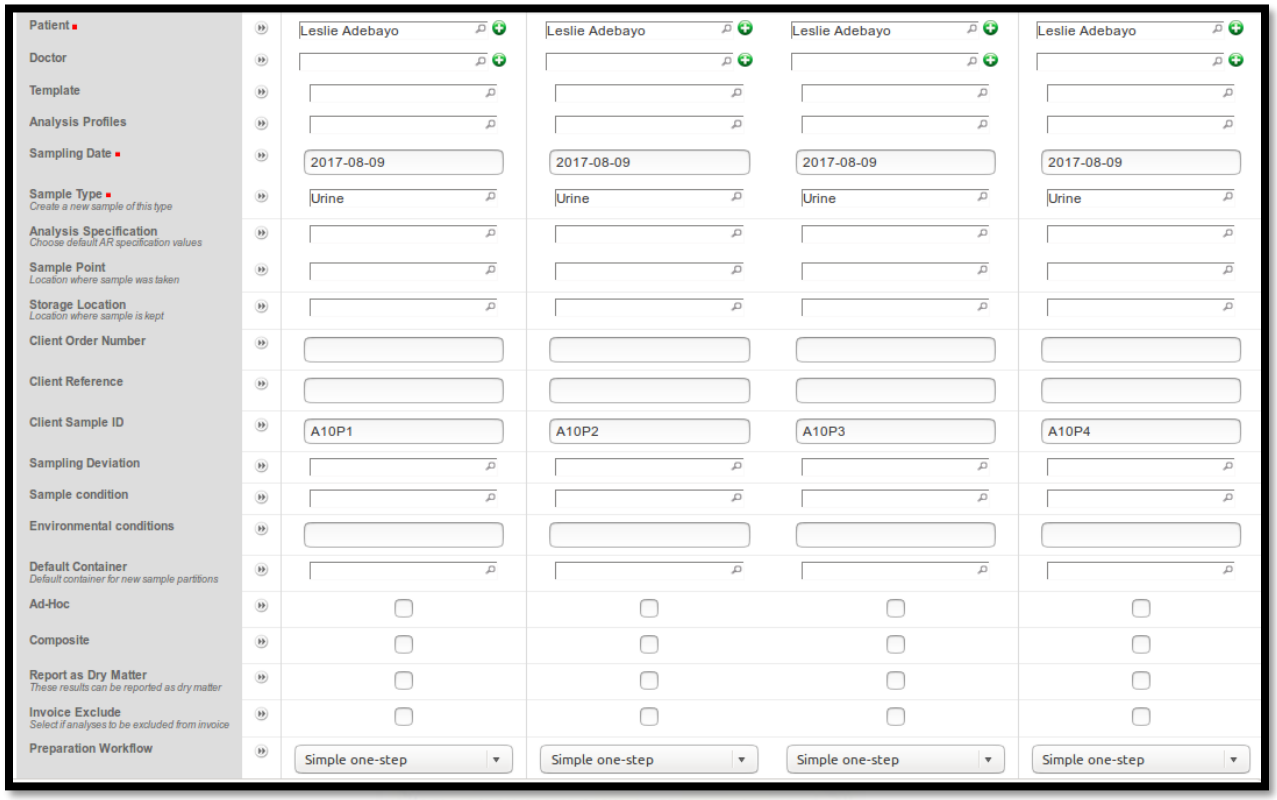
Results

Lab Analyses

Human sample	Result	Value Range
RNA Extraction	17	(RT)

Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

I. Analyses request created for analyses to be carried on samples.



Patient	Leslie Adebayo	Leslie Adebayo	Leslie Adebayo	Leslie Adebayo
Doctor				
Template				
Analysis Profiles				
Sampling Date	2017-08-09	2017-08-09	2017-08-09	2017-08-09
Sample Type Create a new sample of this type	Urine	Urine	Urine	Urine
Analysis Specification Choose default AR specification values				
Sample Point Location where sample was taken				
Storage Location Location where sample is kept				
Client Order Number				
Client Reference				
Client Sample ID	A10P1	A10P2	A10P3	A10P4
Sampling Deviation				
Sample condition				
Environmental conditions				
Default Container Default container for new sample partitions				
Ad-Hoc	☐	☐	☐	☐
Composite	☐	☐	☐	☐
Report as Dry Matter These results can be reported as dry matter	☐	☐	☐	☐
Invoice Exclude Select if analyses to be excluded from invoice	☐	☐	☐	☐
Preparation Workflow	Simple one-step	Simple one-step	Simple one-step	Simple one-step

Lab Analyses

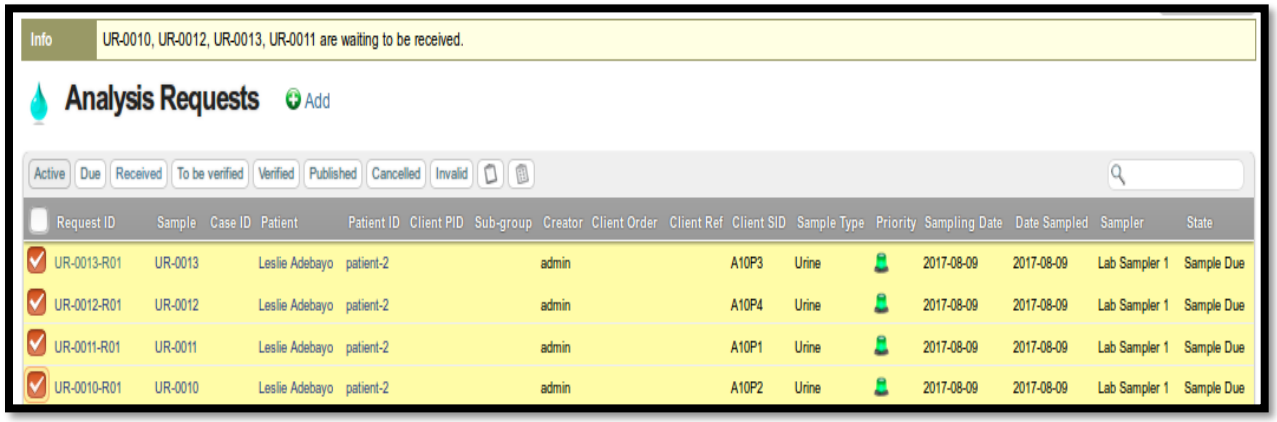
Service	Commercial ID	Protocol ID	AR 0	AR 1	AR 2	AR 3
Human sample						
DNA Extraction			>min <max err% 1	>min <max err% 1	>min <max err% 1	>min <max err% 1
RNA Extraction			>min <max err%	>min <max err%	>min <max err%	>min <max err%

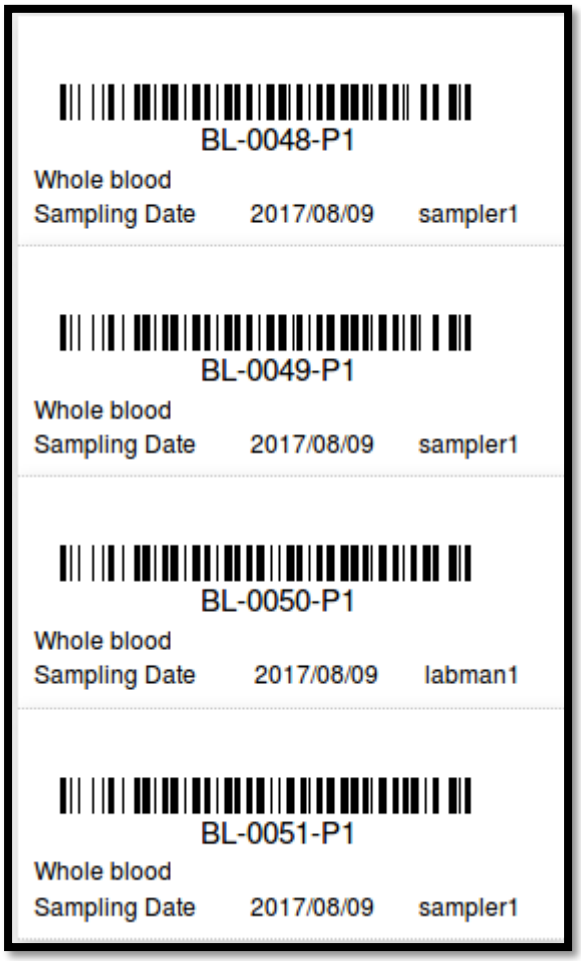
II. Analyses results "BioDropuLITE_data3.csv" file from BioDrop µLITE analytical instrument.

BioDropuLITE_data3.csv

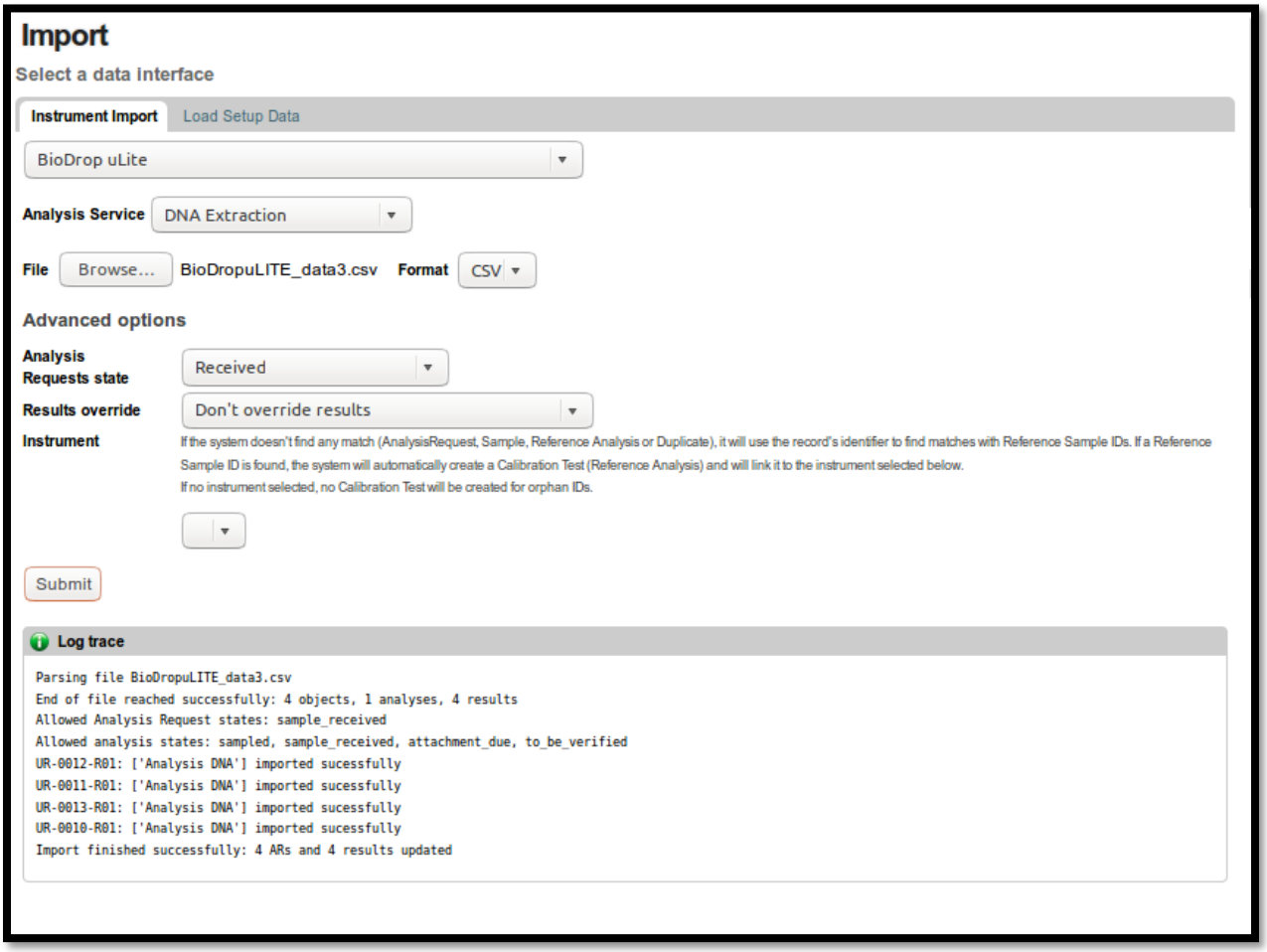
```
Instrument Name,BioDrop µLite,,,,,,,,
Serial Number,1163,,,,,,,,
File Created,03/08/2017,,,,,,,,
Source Application,RNA,,,,,,,,
User,Anon,,,,,,,,
,,,,,,,,,
Pathlength (mm),µLite 0.5mm,,,,,,,,
Bandwidth (nm),1,,,,,,,,
Background,On,,,,,,,,
Dilution Factor,1,,,,,,,,
Integration time (ms),2000,,,,,,,,
Factor,40,,,,,,,,
Units,ng/ul,,,,,,,,
,,,,,,,,,
Date,Time,Sample Name,A230,A260,A280,A320,A260/A230,A260/A280,Concentration
03/08/2017,18:28:00,A10P1,0.019,0.03,0.017,0.003,1.58,1.932,21.559
03/08/2017,18:28:00,A10P2,0.092,0.224,0.108,0.001,2.448,2.082,178.553
03/08/2017,18:28:00,A10P3,0.027,0.059,0.029,0.001,2.231,2.072,46.394
03/08/2017,18:28:00,A10P4,0.023,0.049,0.024,0,2.149,2.058,38.907
```

III. Sample received in the laboratory and barcode are generated for the samples.

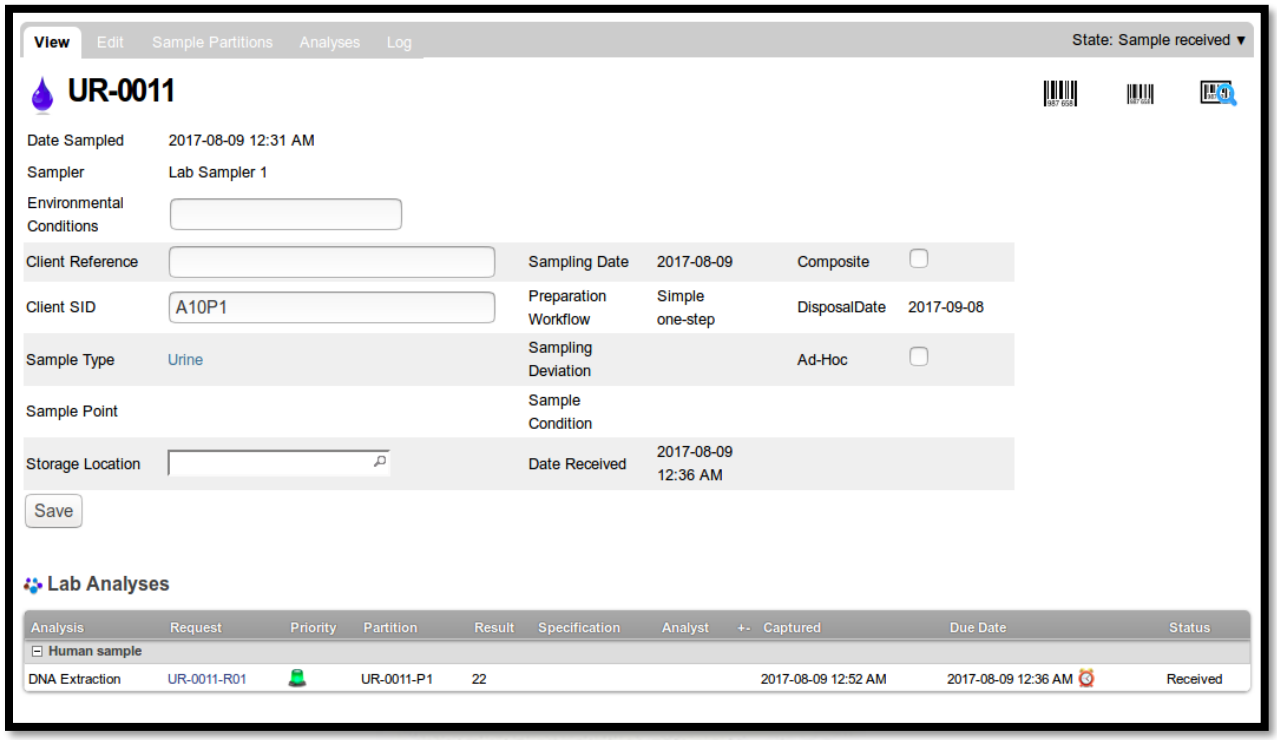




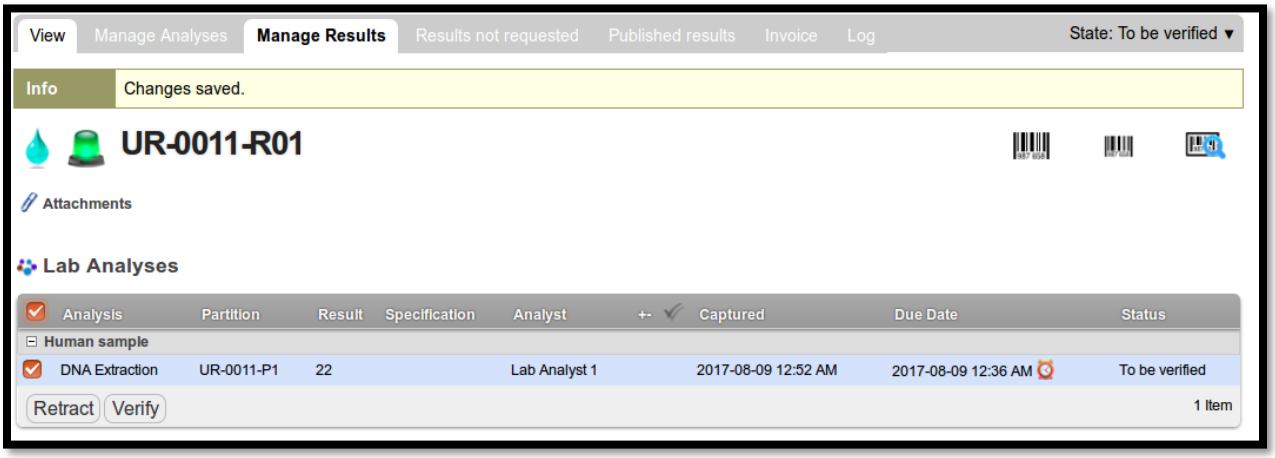
IV. Selection of BioDrop µLITE instrument import interface and DNA concentration results from "BioDropuLITE_data3.csv" file was successfully imported into Bika LIMS.

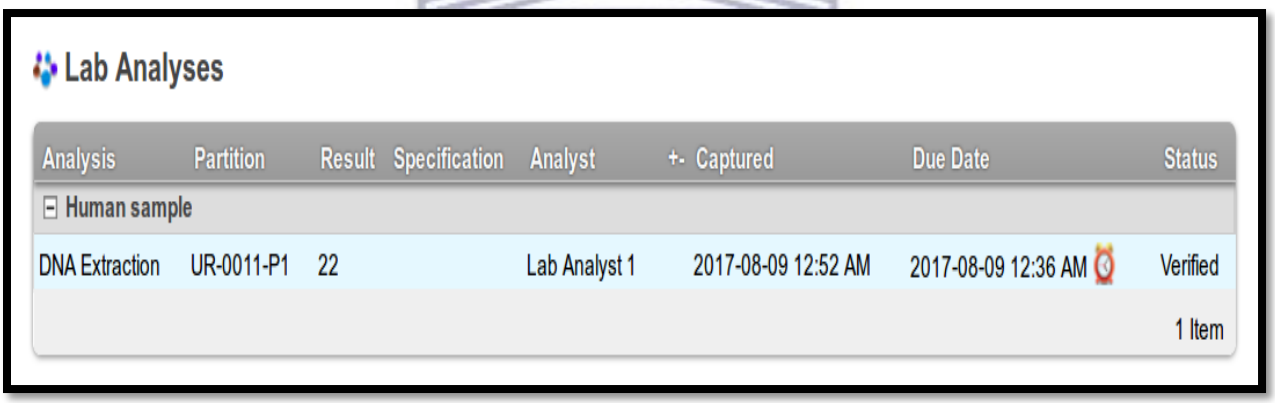


V. DNA analyses results imported for client sample ID "A10P1" from "BioDropuLITE_data3.csv" BioDrop µLITE import interface into Bika LIMS.

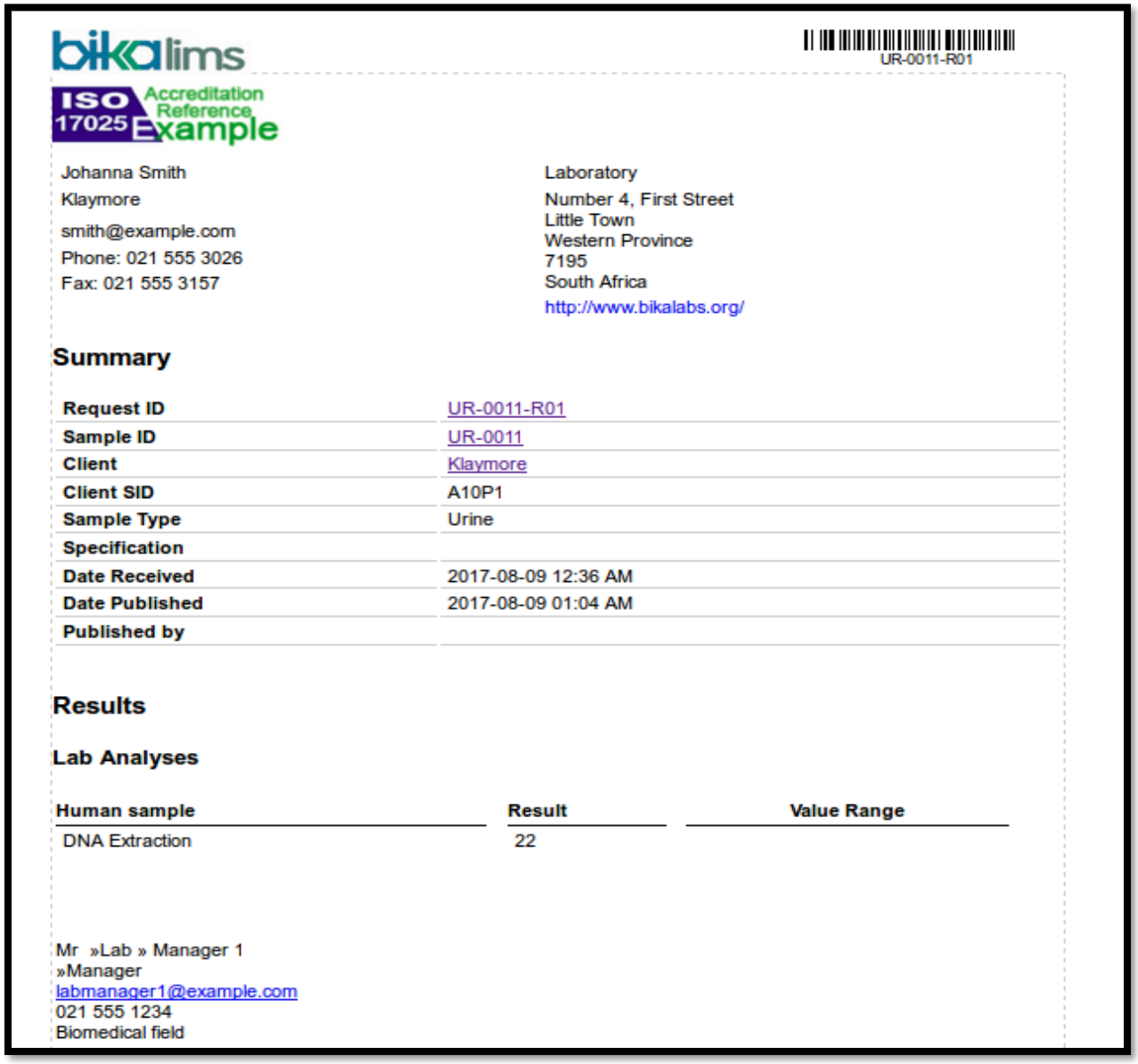


VI. DNA analysis result imported was selected and verification and verified.





VII. DNA concentratiom result for client sample ID “A10P1” was verified and published.



bikalims

UR-0011-R01

ISO 17025 Accreditation Reference Example

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Klaymore
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7195
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Summary

Request ID	UR-0011-R01
Sample ID	UR-0011
Client	Klaymore
Client SID	A10P1
Sample Type	Urine
Specification	
Date Received	2017-08-09 12:36 AM
Date Published	2017-08-09 01:04 AM
Published by	

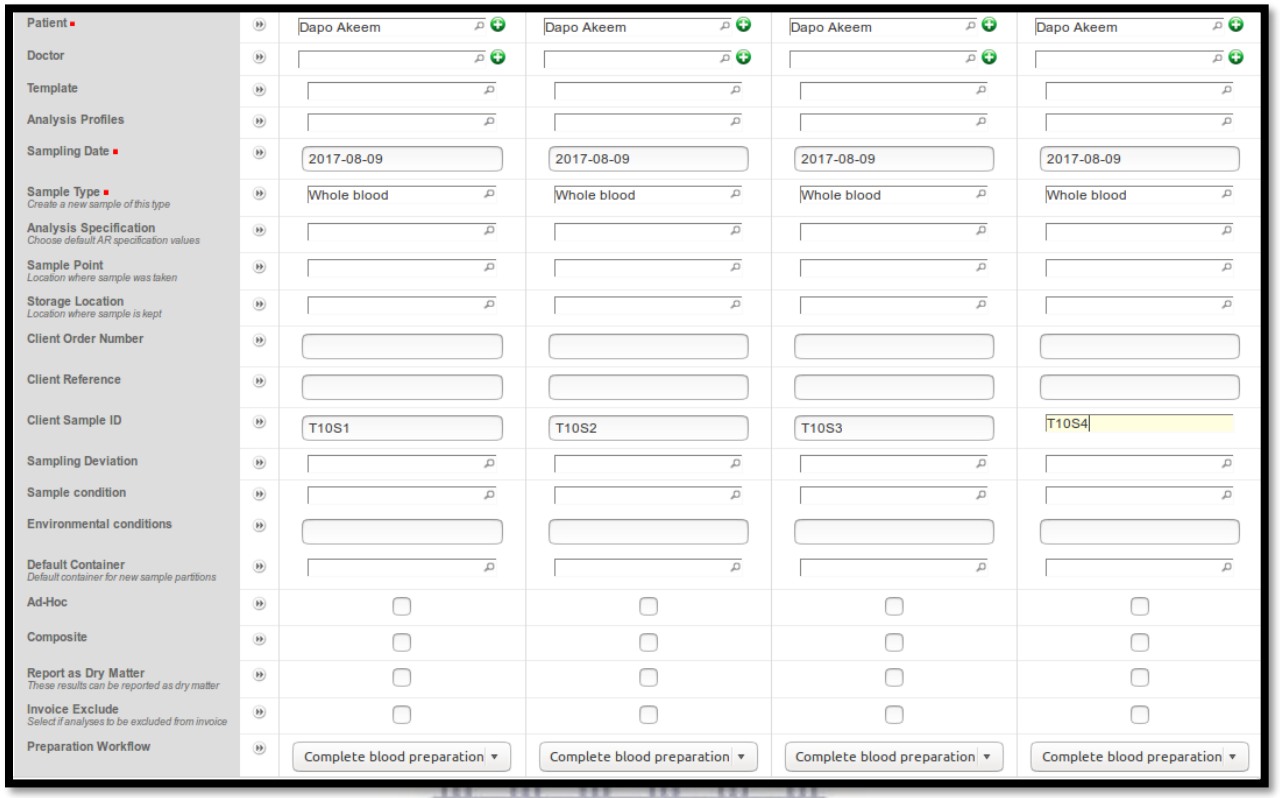
Results

Lab Analyses

Human sample	Result	Value Range
DNA Extraction	22	

Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

I. Analyses request form completed for analyses to be carried on samples



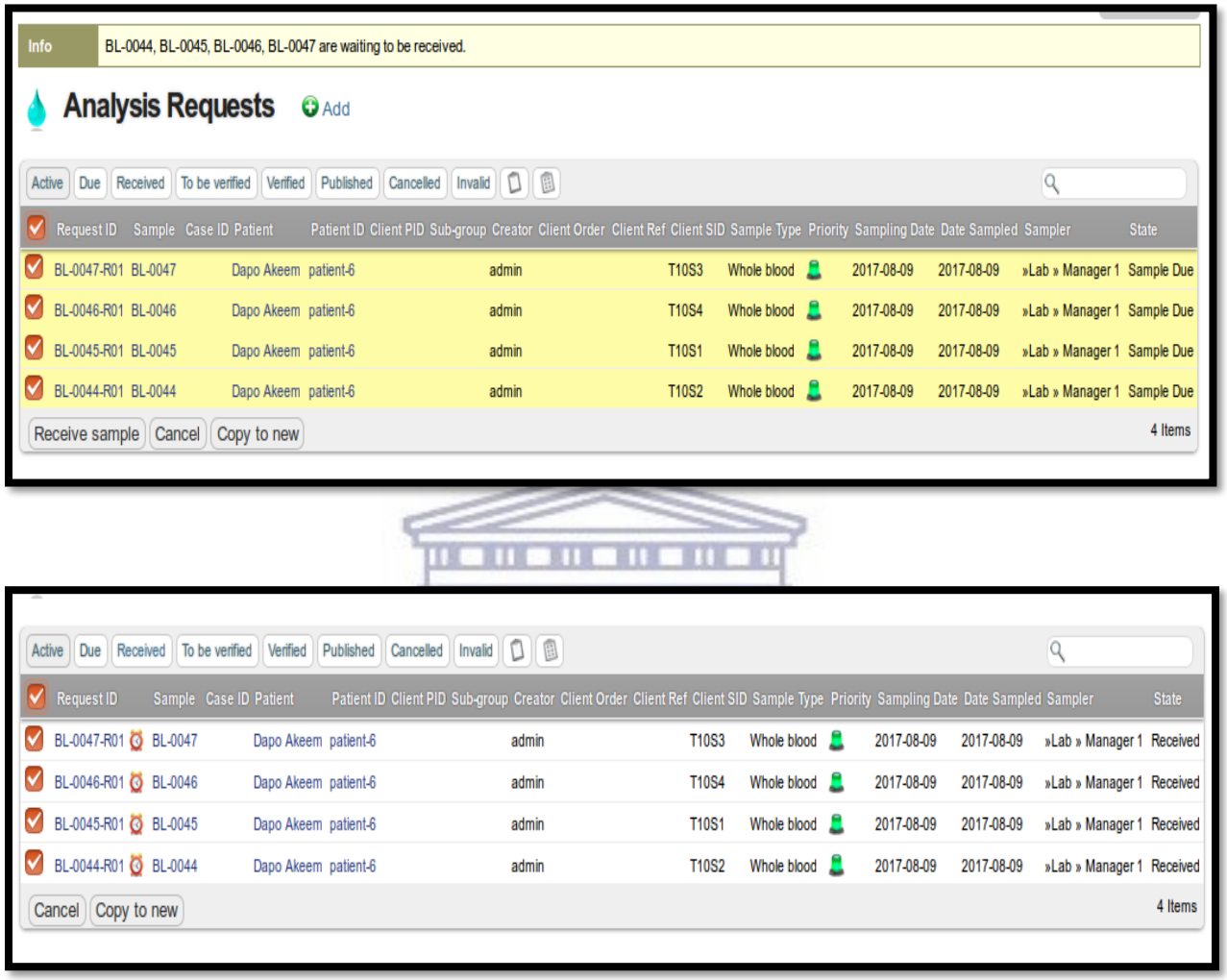
Patient ▪	Dapo Akeem	Dapo Akeem	Dapo Akeem	Dapo Akeem
Doctor				
Template				
Analysis Profiles				
Sampling Date ▪	2017-08-09	2017-08-09	2017-08-09	2017-08-09
Sample Type ▪ *Create a new sample of this type*	Whole blood	Whole blood	Whole blood	Whole blood
Analysis Specification *Choose default AR specification values*				
Sample Point *Location where sample was taken*				
Storage Location *Location where sample is kept*				
Client Order Number				
Client Reference				
Client Sample ID	T10S1	T10S2	T10S3	T10S4
Sampling Deviation				
Sample condition				
Environmental conditions				
Default Container *Default container for new sample partitions*				
Ad-Hoc	☐	☐	☐	☐
Composite	☐	☐	☐	☐
Report as Dry Matter *These results can be reported as dry matter*	☐	☐	☐	☐
Invoice Exclude *Select if analyses to be excluded from invoice*	☐	☐	☐	☐
Preparation Workflow	Complete blood preparation	Complete blood preparation	Complete blood preparation	Complete blood preparation

II. BioDrop µLITE instrument data structure and format. (BioDropuLITE_data4.csv) in CSV file format and structure, the concentration results in the analysis data must be captured into BikaLIMS

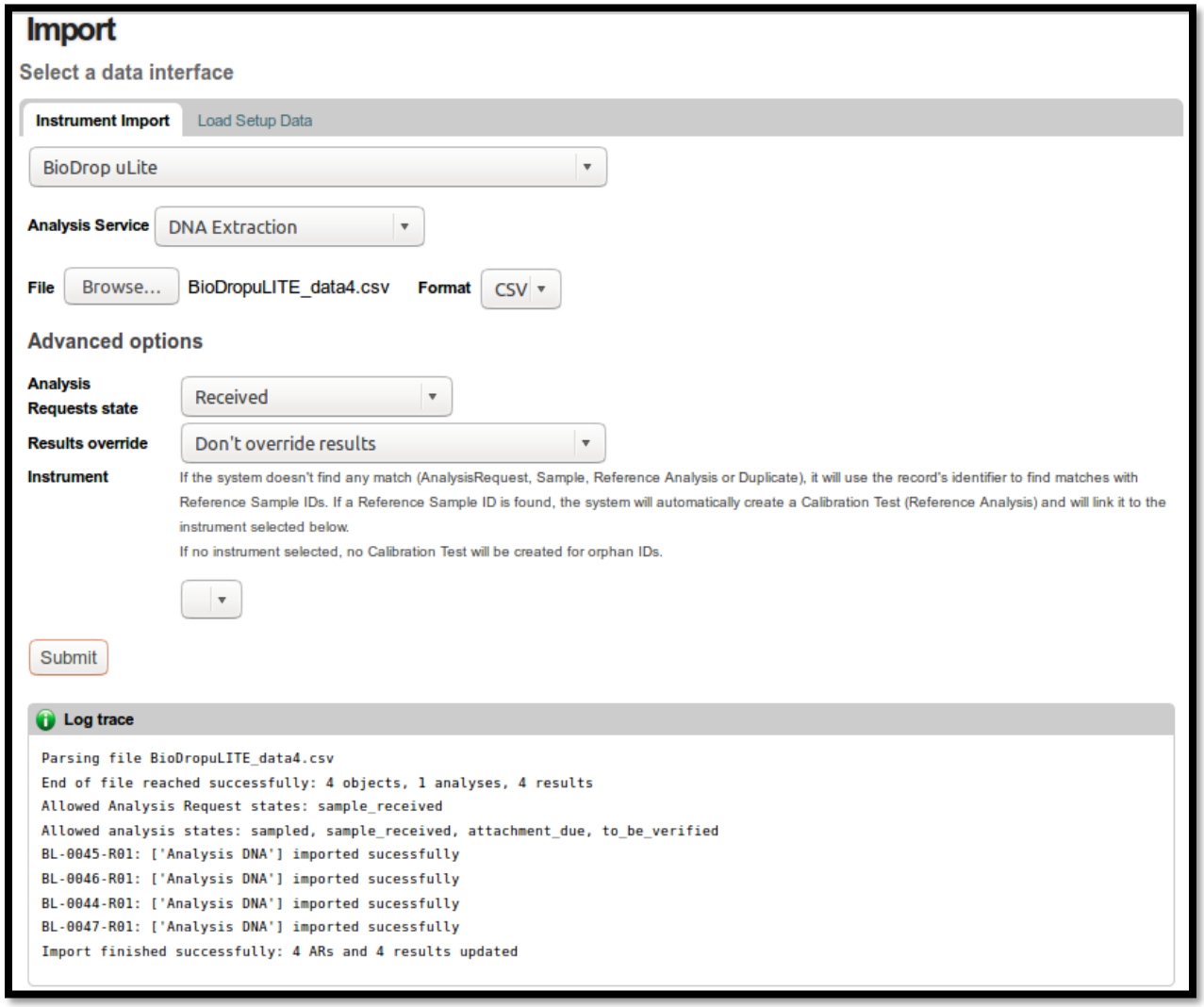
BioDropuLITE_data4.csv

```
Instrument Name,BioDrop µLite,,,,,,,,
Serial Number,1163,,,,,,,,
File Created,04/08/2017,,,,,,,,
Source Application,RNA,,,,,,,,
User,Anon,,,,,,,,
,,,,,,,,,
Pathlength (mm),µLite 0.5mm,,,,,,,,
Bandwidth (nm),1,,,,,,,,
Background,On,,,,,,,,
Dilution Factor,1,,,,,,,,
Integration time (ms),2000,,,,,,,,
Factor,40,,,,,,,,
Units,ng/ul,,,,,,,,
,,,,,,,,,
Date,Time,Sample Name,A230,A260,A280,A320,A260/A230,A260/A280,Concentration
04/08/2017,07:24:00,T10S1,0.039,0.07,0.037,0.007,1.89,1.89,41.83
04/08/2017,07:24:00,T10S2,0.072,0.224,0.114,0.003,3.11,1.96,11.53
04/08/2017,07:24:00,T10S3,0.047,0.036,0.059,0.002,0.77,0.61,35.36
04/08/2017,07:24:00,T10S4,0.083,0.036,0.054,5,0.43,0.67,26.59
```

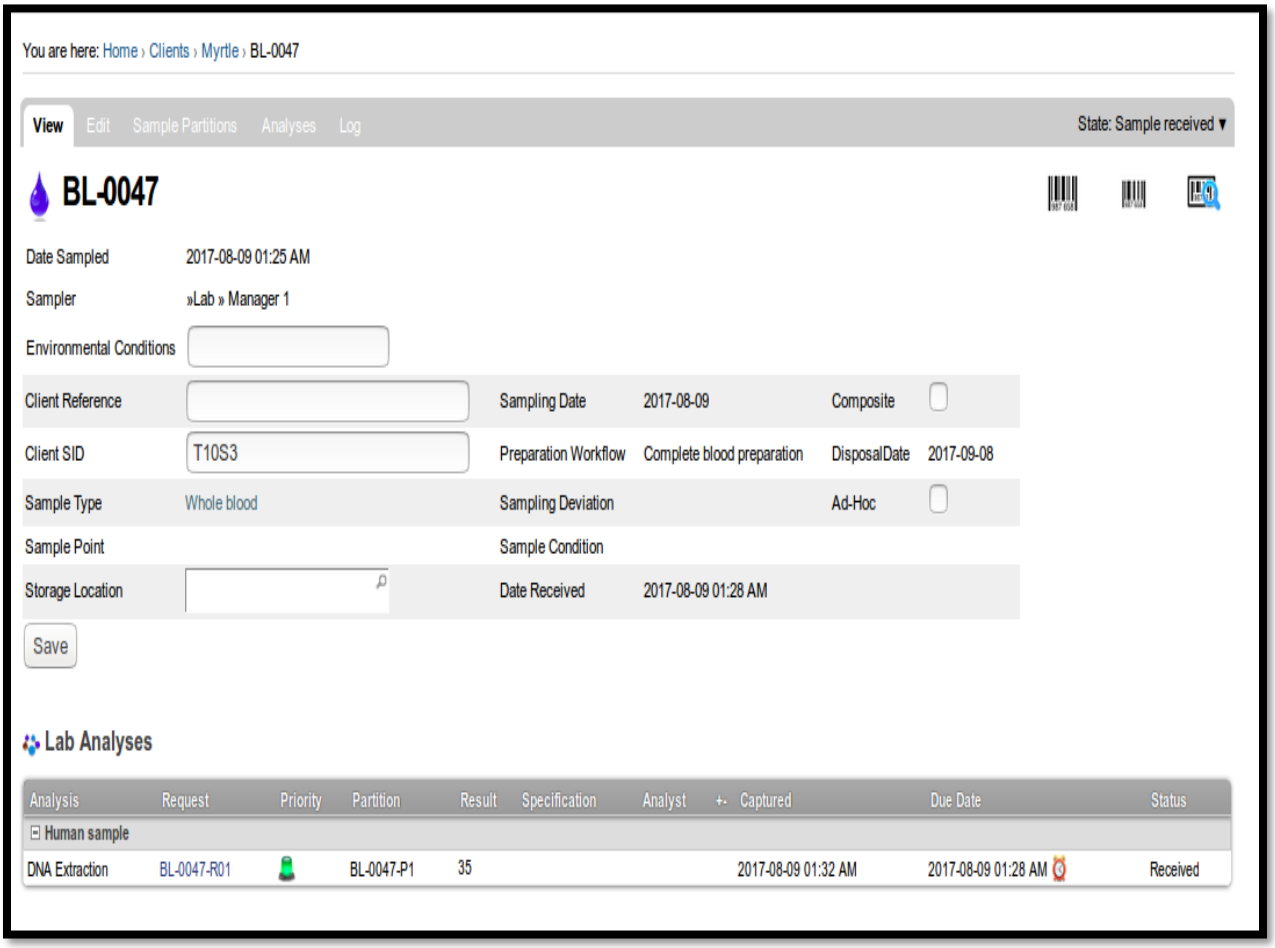
III. Analysis request in sample due state. The sample was received into the laboratory for analyses.



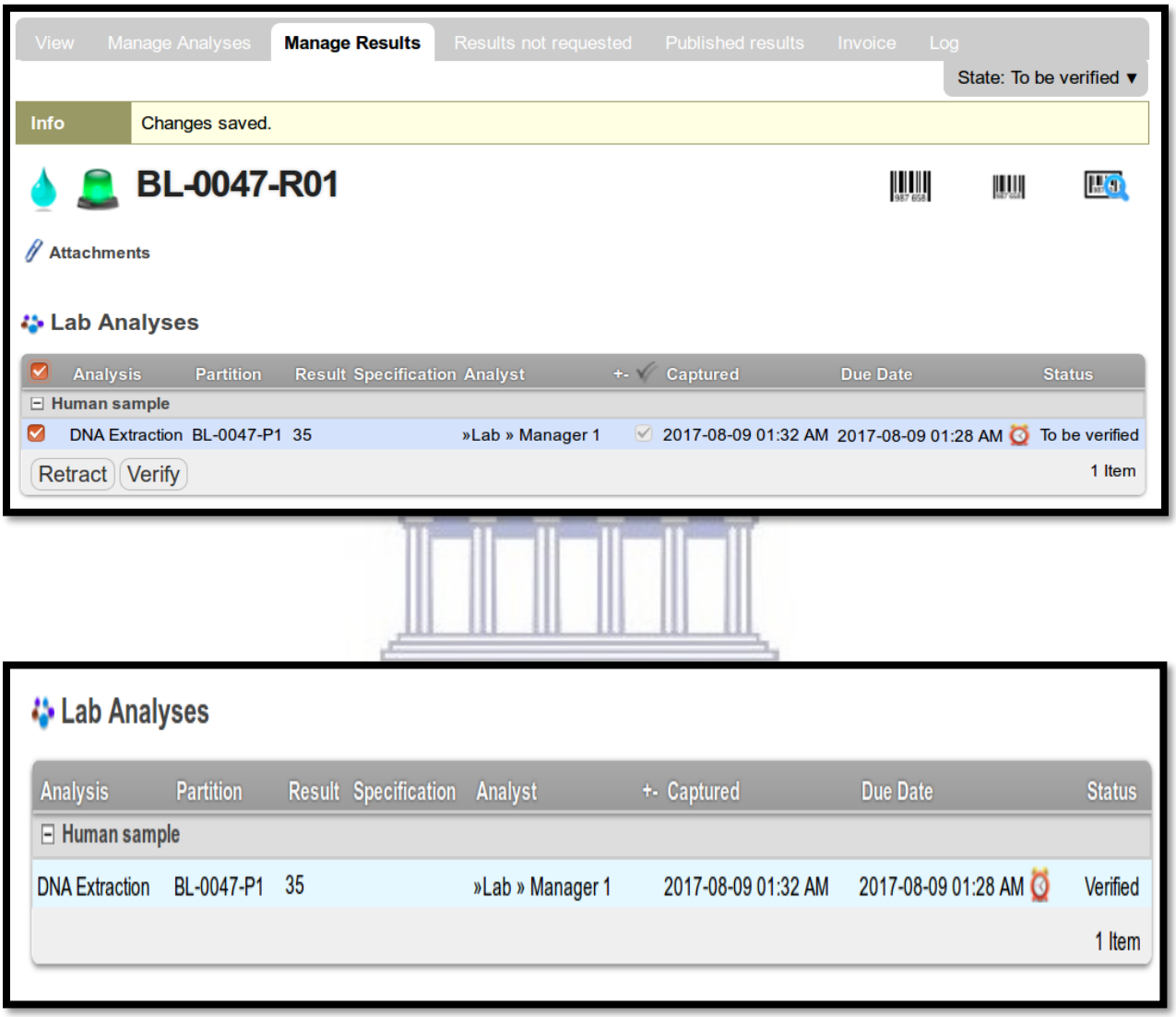
IV. Selection of BioDrop µLITE instrument import interface and DNA concentration results from “BioDropuLITE_data4.csv” file was successfully imported into Bika LIMS.



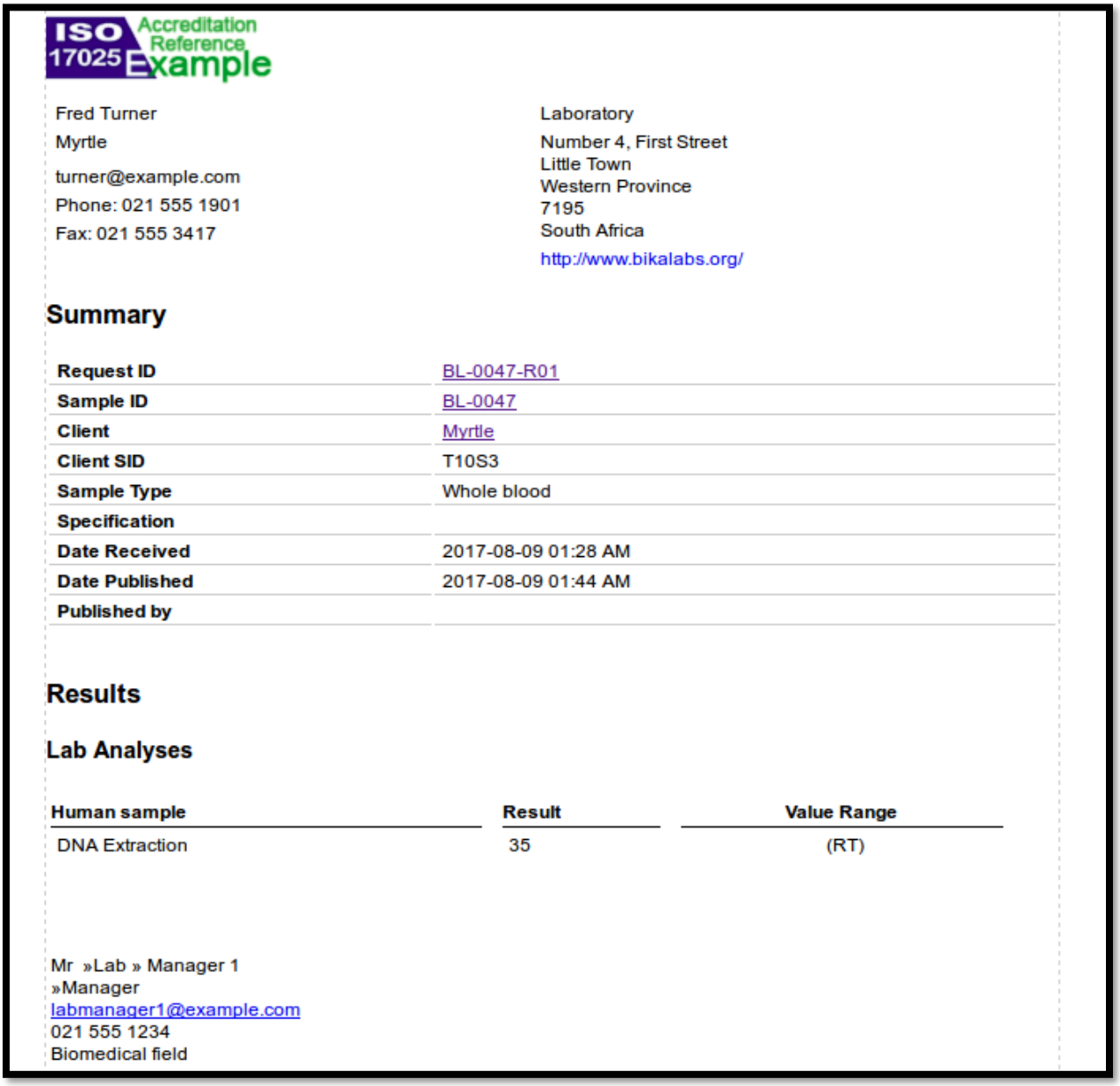
V. DNA analyses results imported for client sample ID "T10S3" from "BioDropuLITE_data4.csv" BioDrop µLITE import interface into Bika LIMS



VI. The concentration analysis result with client sample ID “T10S3” was verified by selection for verification.



VII. RNA concentration result for client ID “T10S3” published.



ISO 17025 Accreditation Reference Example

Fred Turner
Myrtle
turner@example.com
Phone: 021 555 1901
Fax: 021 555 3417

Laboratory
Number 4, First Street
Little Town
Western Province
7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	BL-0047-R01
Sample ID	BL-0047
Client	Myrtle
Client SID	T10S3
Sample Type	Whole blood
Specification	
Date Received	2017-08-09 01:28 AM
Date Published	2017-08-09 01:44 AM
Published by	

Results

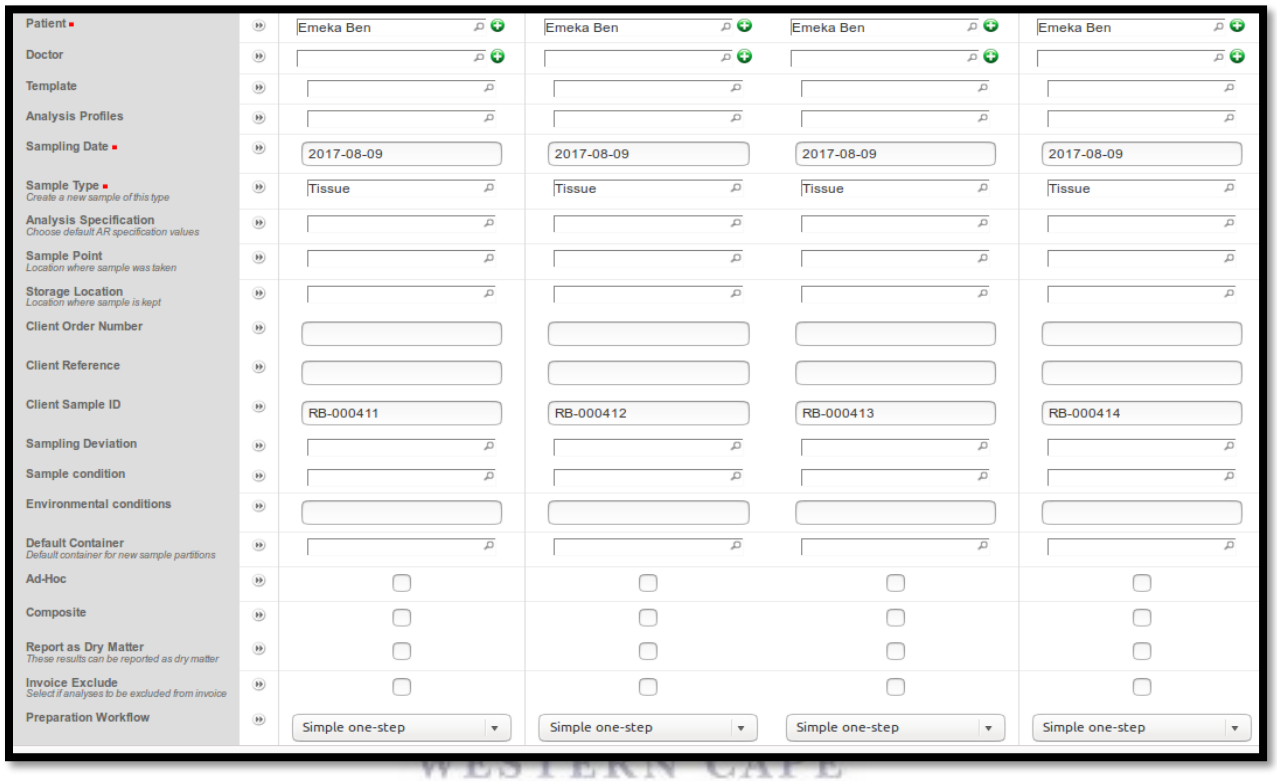
Lab Analyses

Human sample	Result	Value Range
DNA Extraction	35	(RT)

Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

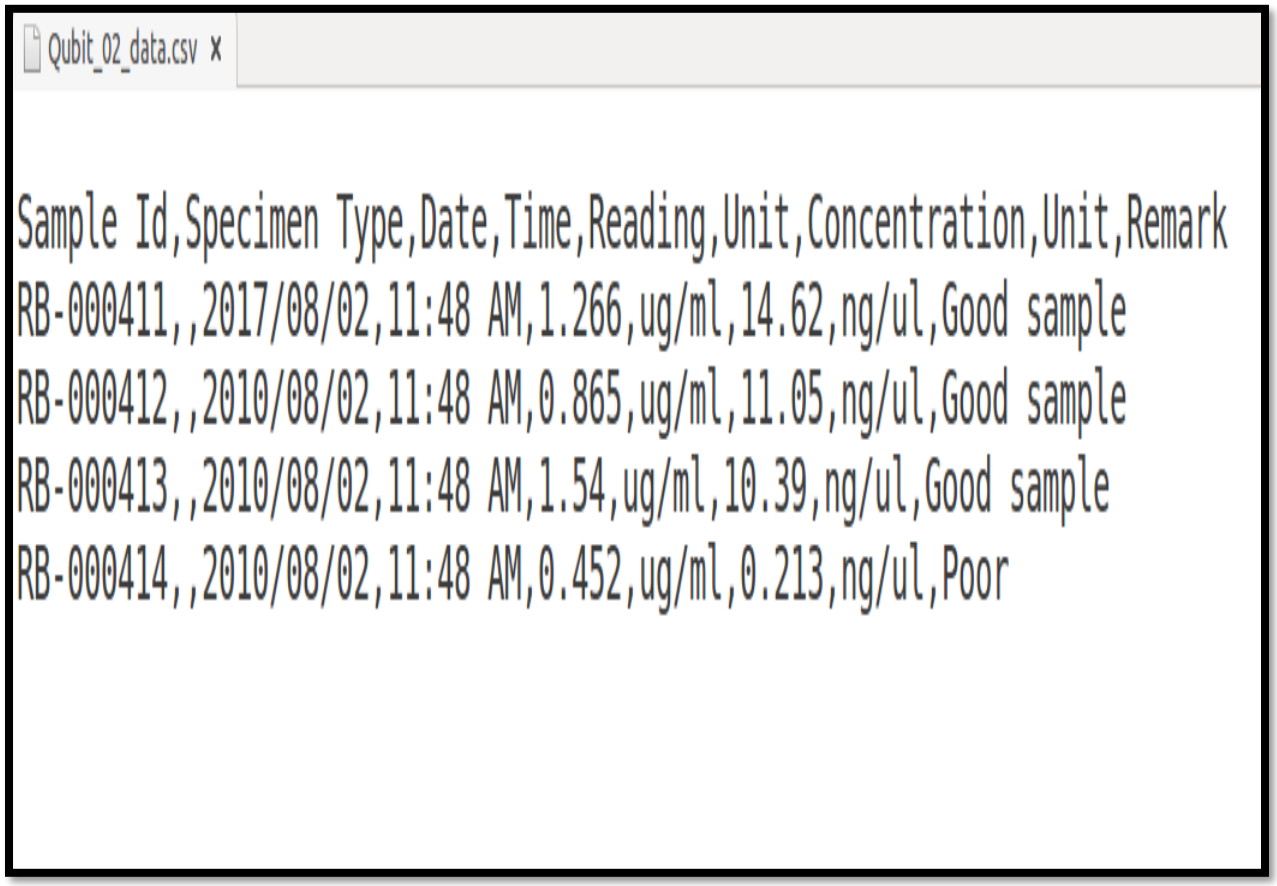
Appendix E: Test results for importation of analyses results from Qubit Fluorometer instrument file and management of sample

I. Analyses request created for analyses to be carried on samples

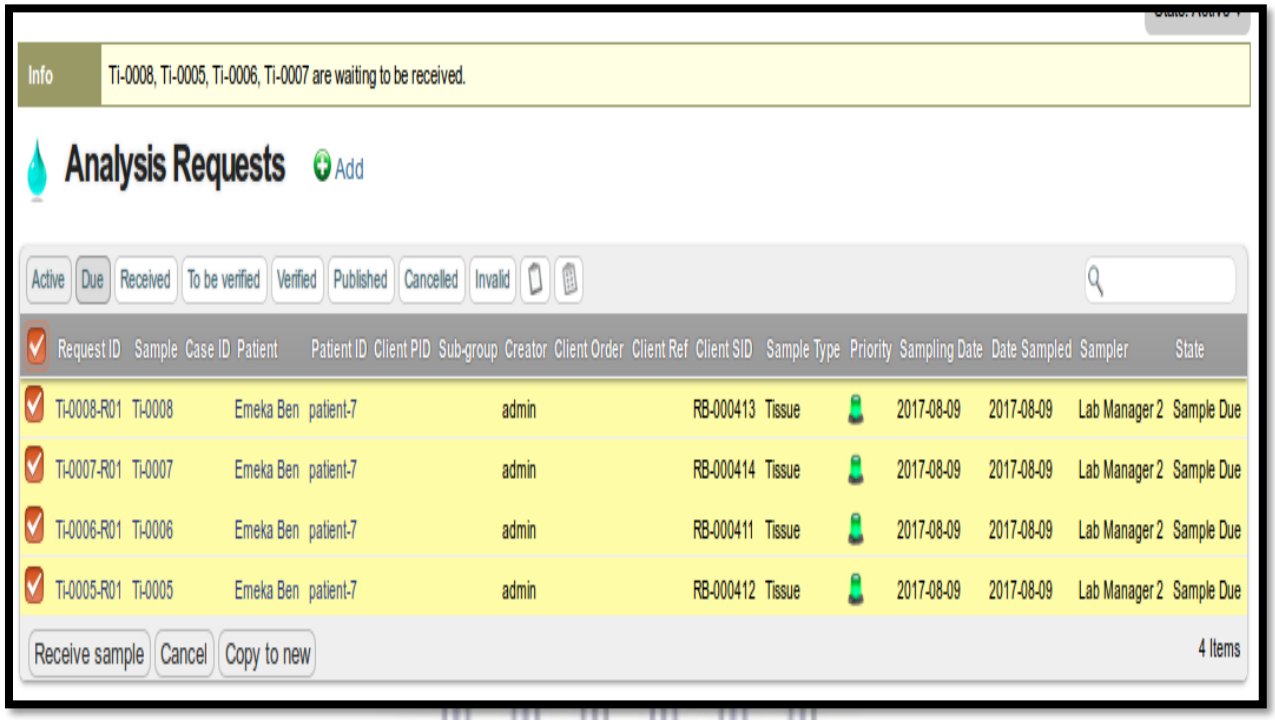


Patient	Emeka Ben	Emeka Ben	Emeka Ben	Emeka Ben
Doctor				
Template				
Analysis Profiles				
Sampling Date	2017-08-09	2017-08-09	2017-08-09	2017-08-09
Sample Type Create a new sample of this type	Tissue	Tissue	Tissue	Tissue
Analysis Specification Choose default AR specification values				
Sample Point Location where sample was taken				
Storage Location Location where sample is kept				
Client Order Number				
Client Reference				
Client Sample ID	RB-000411	RB-000412	RB-000413	RB-000414
Sampling Deviation				
Sample condition				
Environmental conditions				
Default Container Default container for new sample partitions				
Ad-Hoc	☐	☐	☐	☐
Composite	☐	☐	☐	☐
Report as Dry Matter These results can be reported as dry matter	☐	☐	☐	☐
Invoice Exclude Select if analyses to be excluded from invoice	☐	☐	☐	☐
Preparation Workflow	Simple one-step	Simple one-step	Simple one-step	Simple one-step

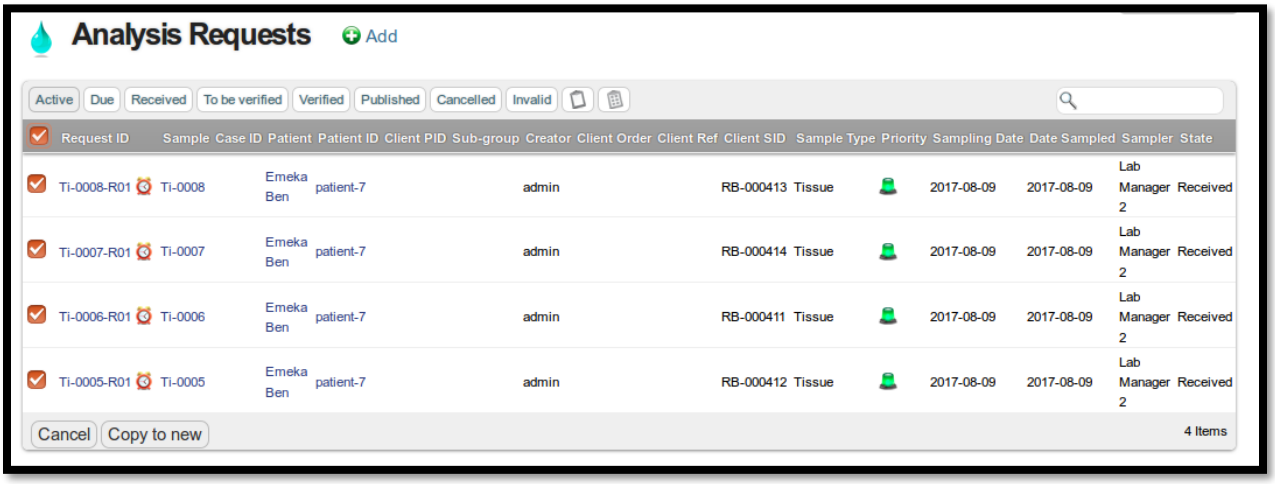
II. Qubit Fluorometer instrument data structure and format. (Qubit_02_data.csv) in CSV file format and structure, the concentration results analysis data must be captured into BikaLIMS

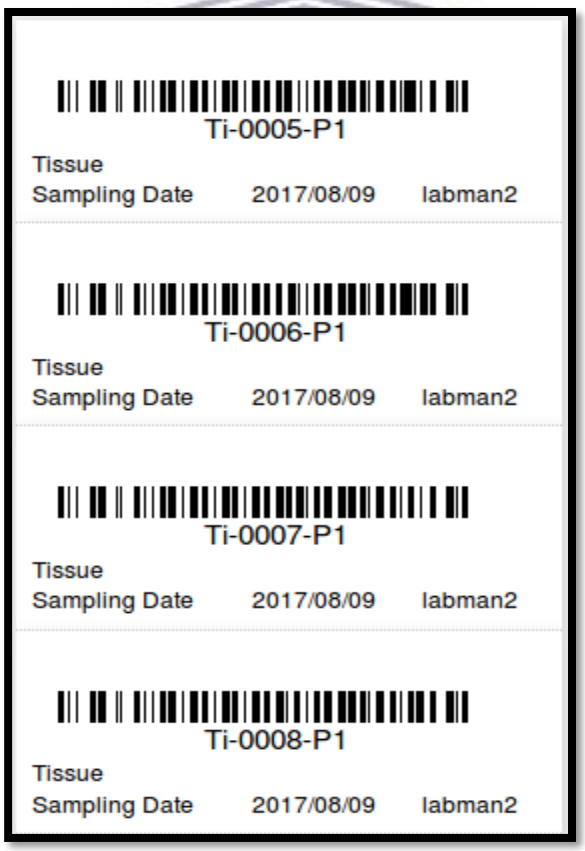


III. Analysis requested to be carried out in “sample due” state.

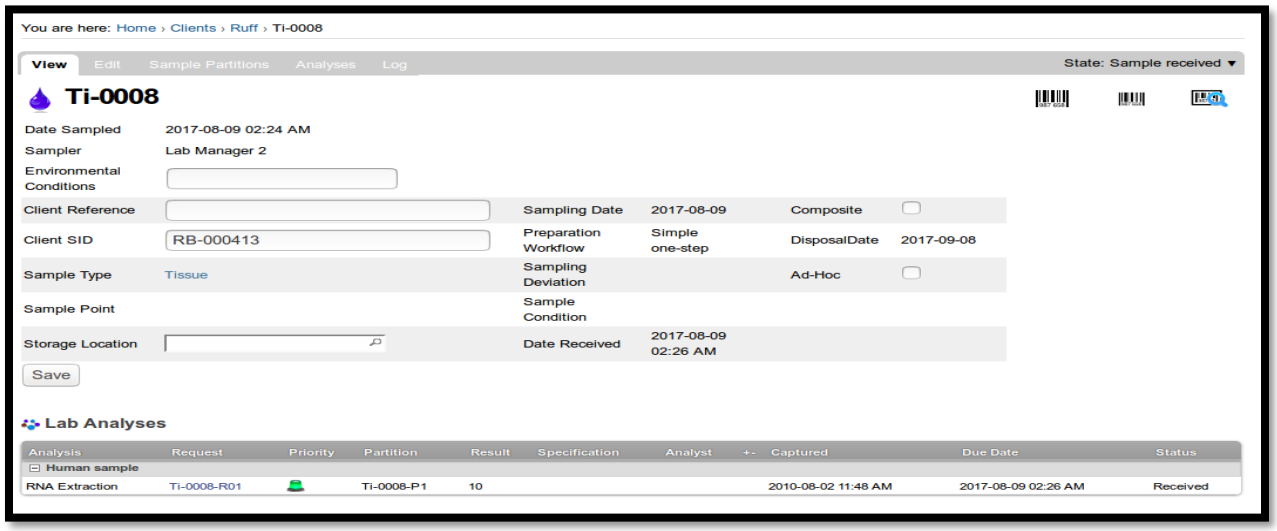


IV. A unique barcode generated by the LIMS for each sample received

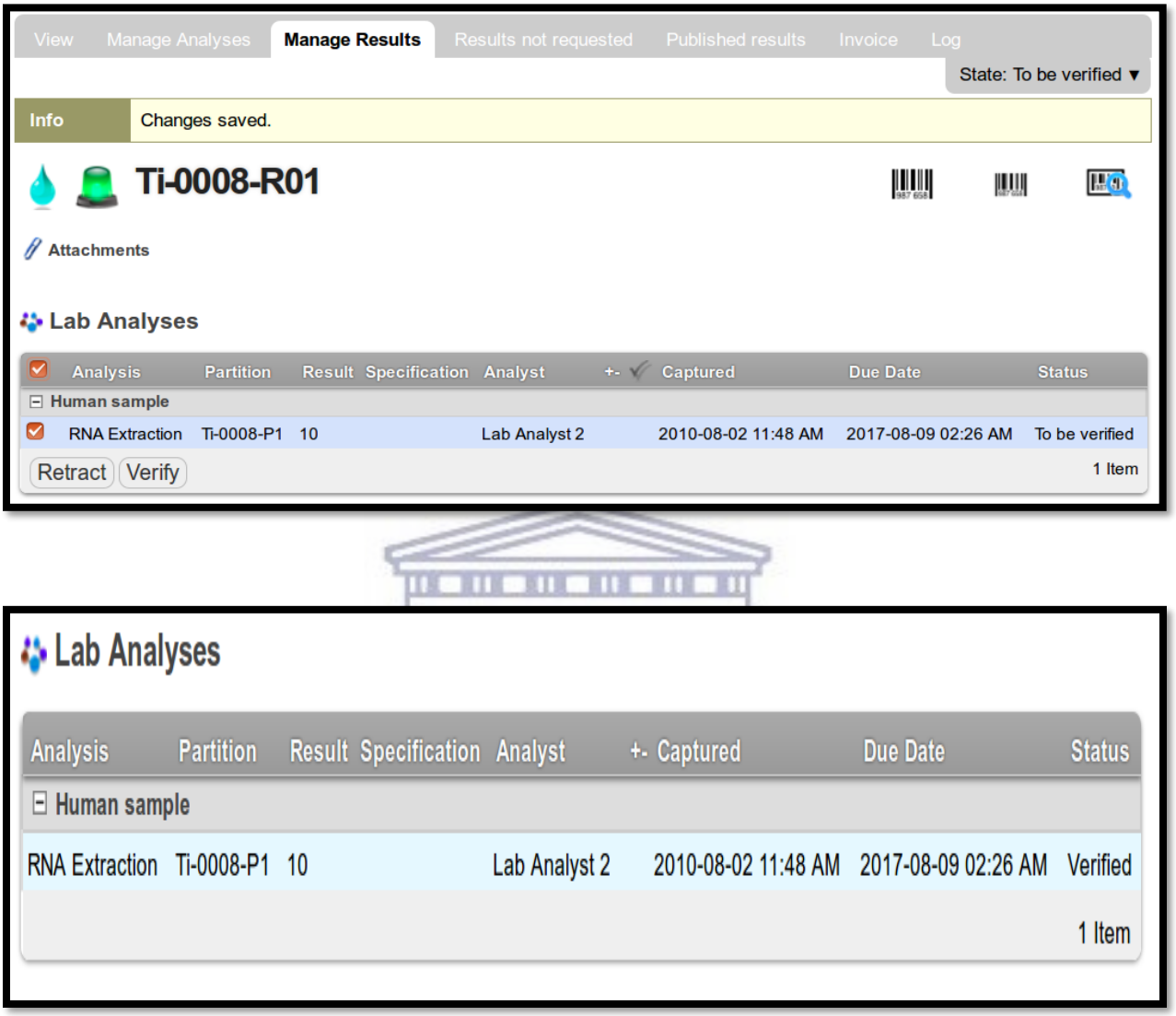




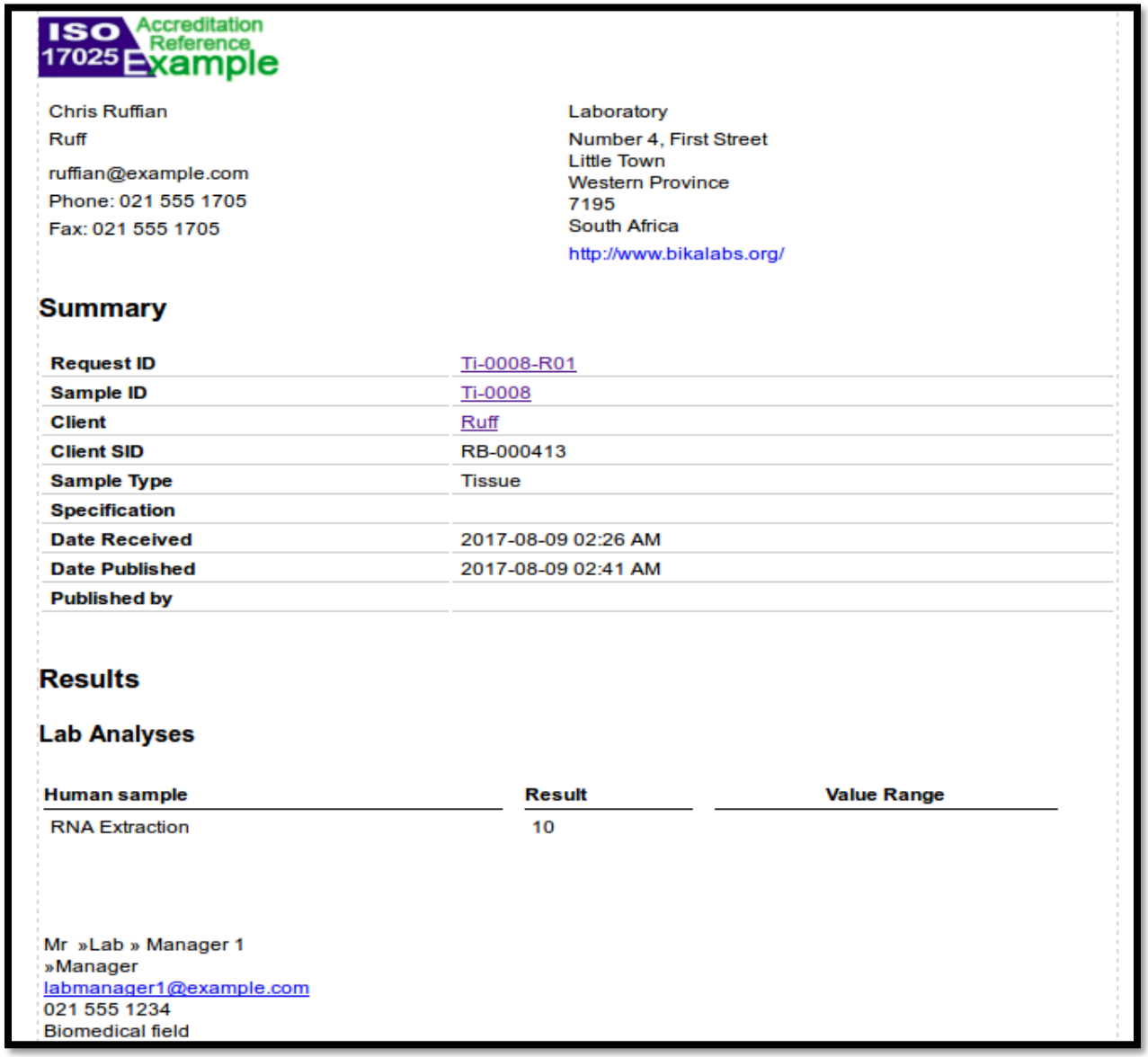
V. Qubit_02_data.csv concentration results imported into Bika LIMS. RNA concentration result for client sample ID “RB-00043” with barcode “Ti-0008” and sample information linked with the sample preparation option “simple one-step”.



VI. The concentration analysis result was verified by selection for verification.



VII. RNA concentration result for client ID “RB-000413” published.



ISO 17025 Accreditation Reference Example

Chris Ruffian
Ruff
ruffian@example.com
Phone: 021 555 1705
Fax: 021 555 1705

Laboratory
Number 4, First Street
Little Town
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7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	Ti-0008-R01
Sample ID	Ti-0008
Client	Ruff
Client SID	RB-000413
Sample Type	Tissue
Specification	
Date Received	2017-08-09 02:26 AM
Date Published	2017-08-09 02:41 AM
Published by	

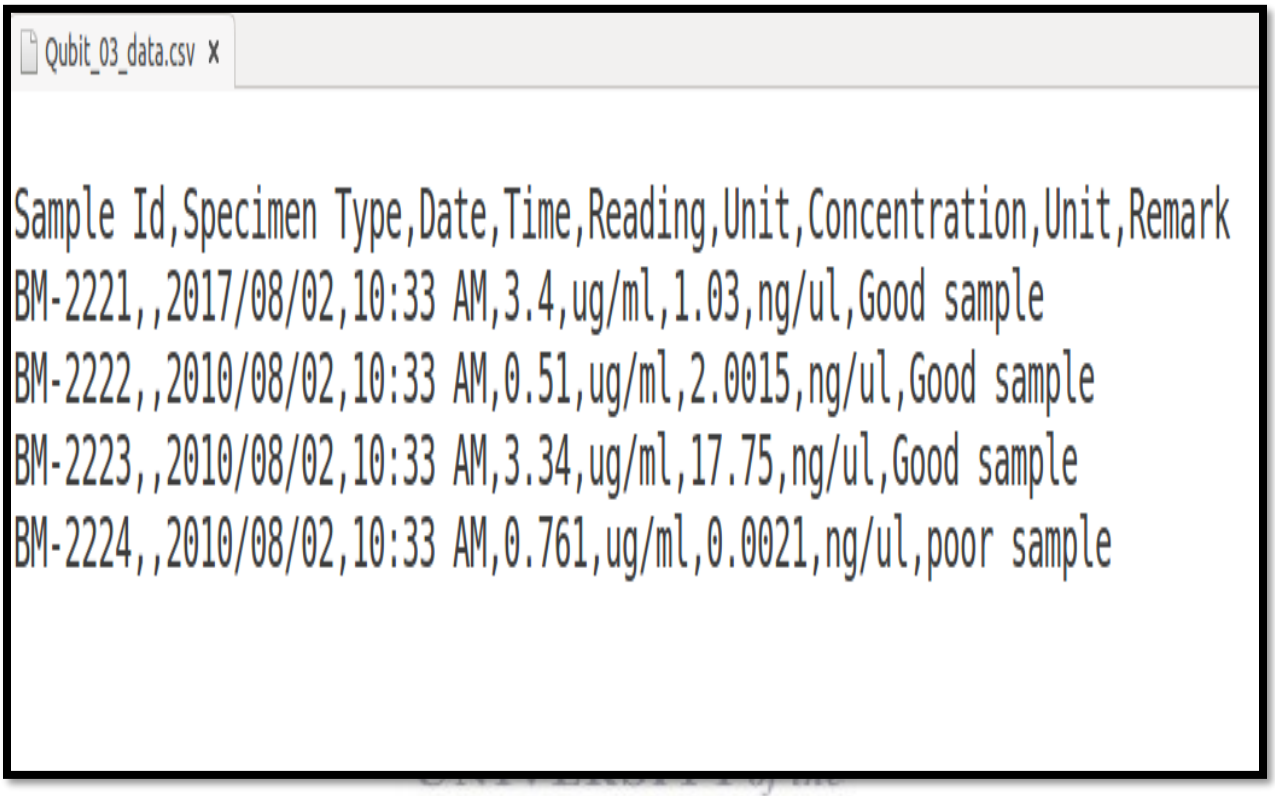
Results

Lab Analyses

Human sample	Result	Value Range
RNA Extraction	10	

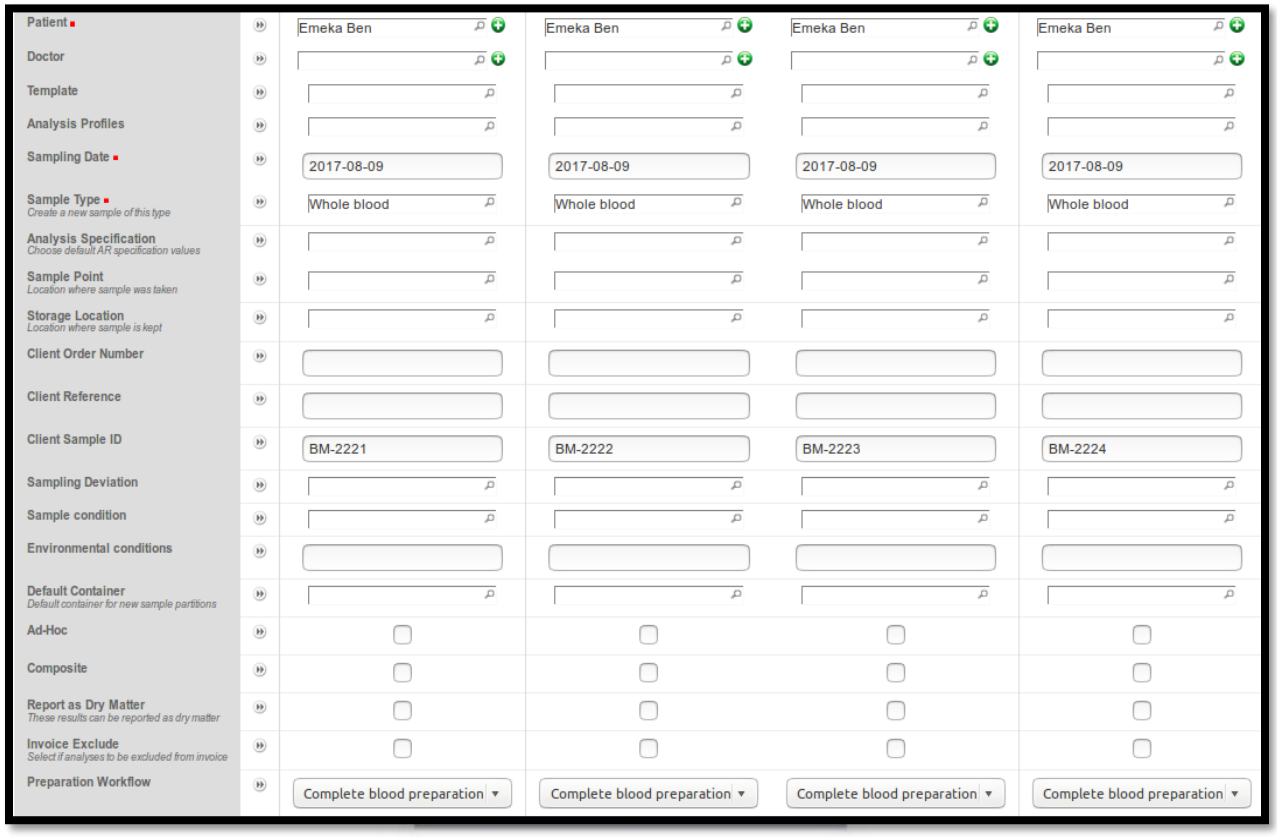
Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

VIII. Qubit_03_data.csv was concentration results file obtained from Qubit Fluorometer instrument.


Qubit_03_data.csv

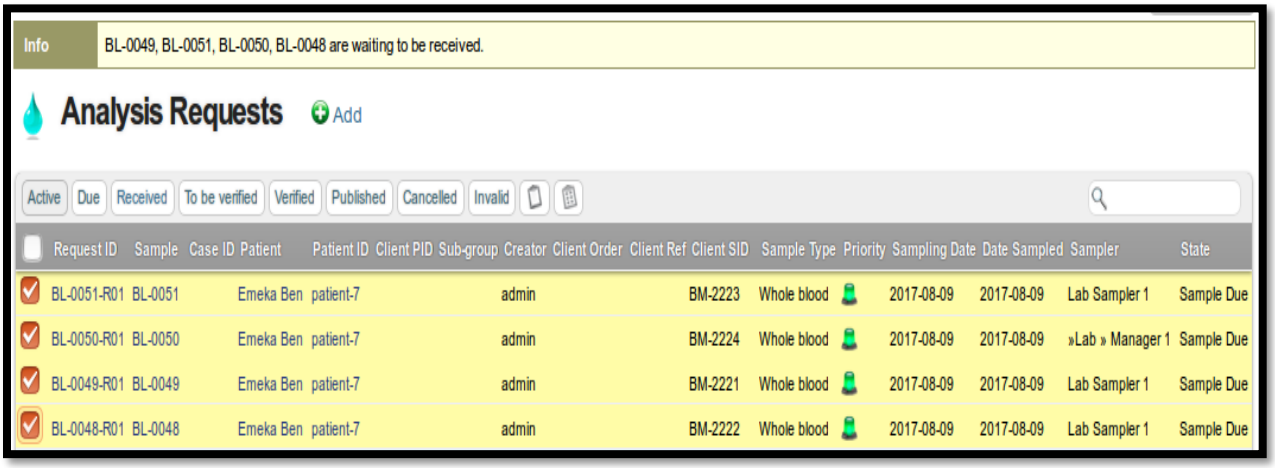
```
Sample Id,Specimen Type,Date,Time,Reading,Unit,Concentration,Unit,Remark
BM-2221,,2017/08/02,10:33 AM,3.4,ug/ml,1.03,ng/ul,Good sample
BM-2222,,2010/08/02,10:33 AM,0.51,ug/ml,2.0015,ng/ul,Good sample
BM-2223,,2010/08/02,10:33 AM,3.34,ug/ml,17.75,ng/ul,Good sample
BM-2224,,2010/08/02,10:33 AM,0.761,ug/ml,0.0021,ng/ul,poor sample
```

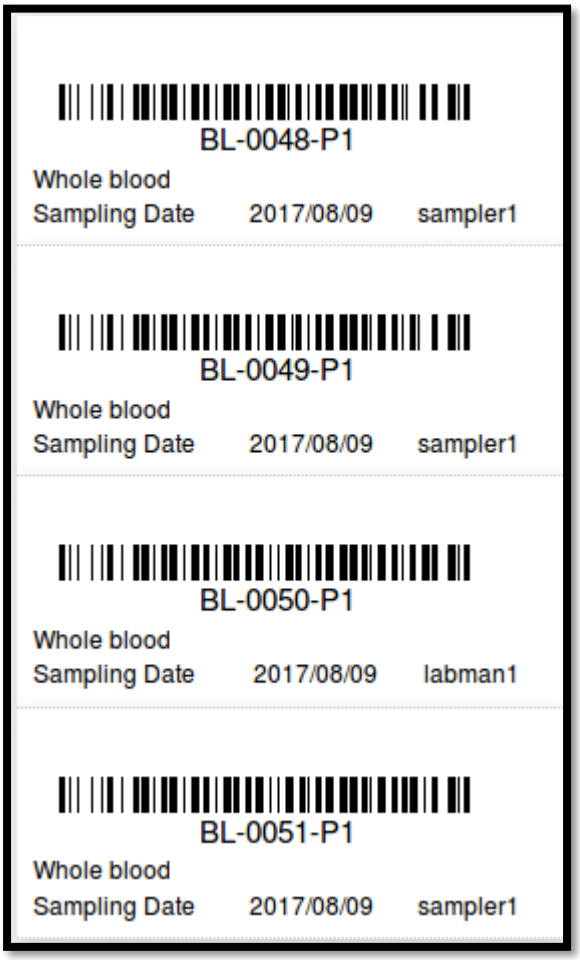
I. Analyses request form completed for analyses to be carried on samples



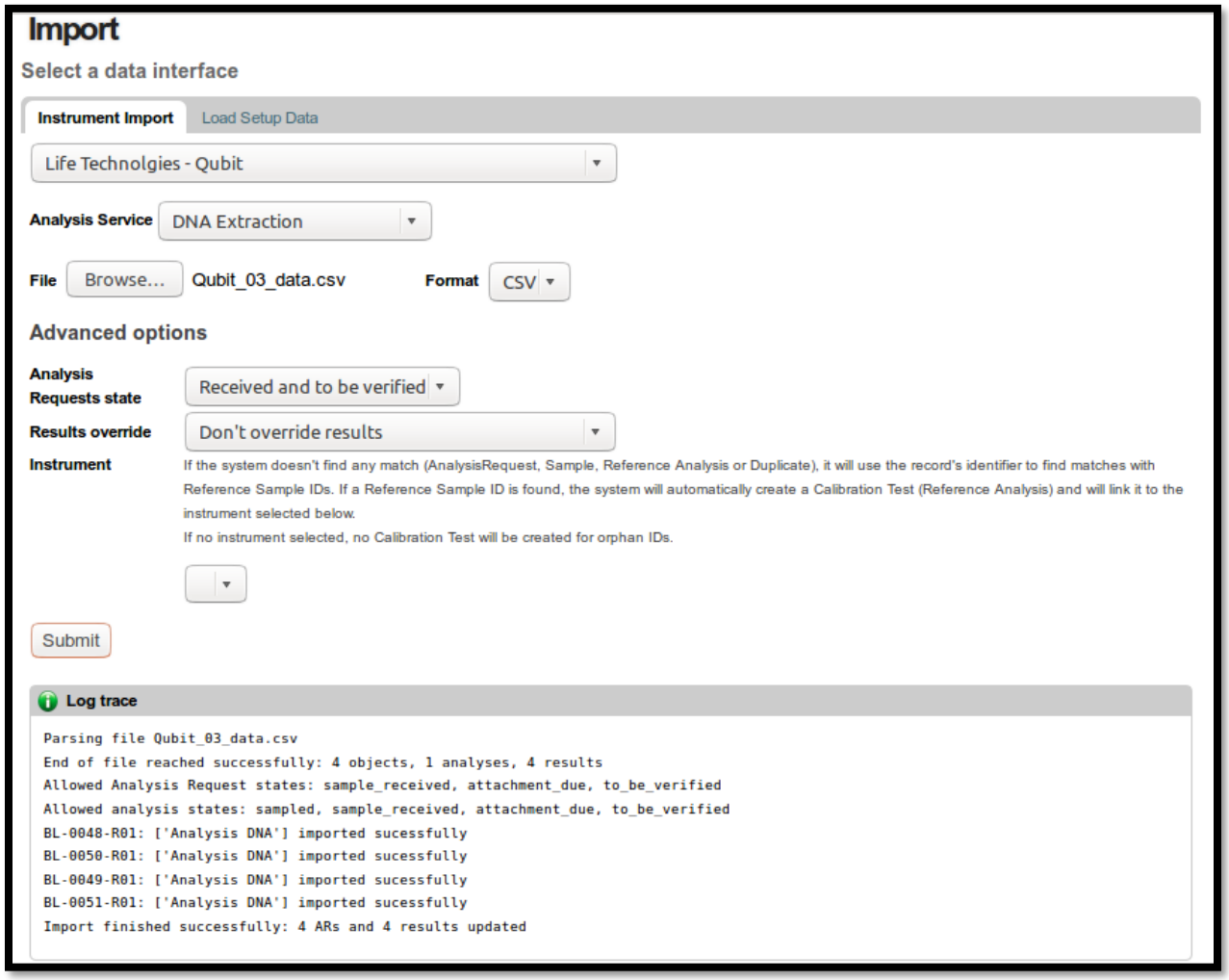
Patient	Emeka Ben	Emeka Ben	Emeka Ben	Emeka Ben
Doctor				
Template				
Analysis Profiles				
Sampling Date	2017-08-09	2017-08-09	2017-08-09	2017-08-09
Sample Type Create a new sample of this type	Whole blood	Whole blood	Whole blood	Whole blood
Analysis Specification Choose default AR specification values				
Sample Point Location where sample was taken				
Storage Location Location where sample is kept				
Client Order Number				
Client Reference				
Client Sample ID	BM-2221	BM-2222	BM-2223	BM-2224
Sampling Deviation				
Sample condition				
Environmental conditions				
Default Container Default container for new sample partitions				
Ad-Hoc	☐	☐	☐	☐
Composite	☐	☐	☐	☐
Report as Dry Matter These results can be reported as dry matter	☐	☐	☐	☐
Invoice Exclude Select if analyses to be excluded from invoice	☐	☐	☐	☐
Preparation Workflow	Complete blood preparation	Complete blood preparation	Complete blood preparation	Complete blood preparation

II. Sample received in the laboratory and barcode are generated for the samples

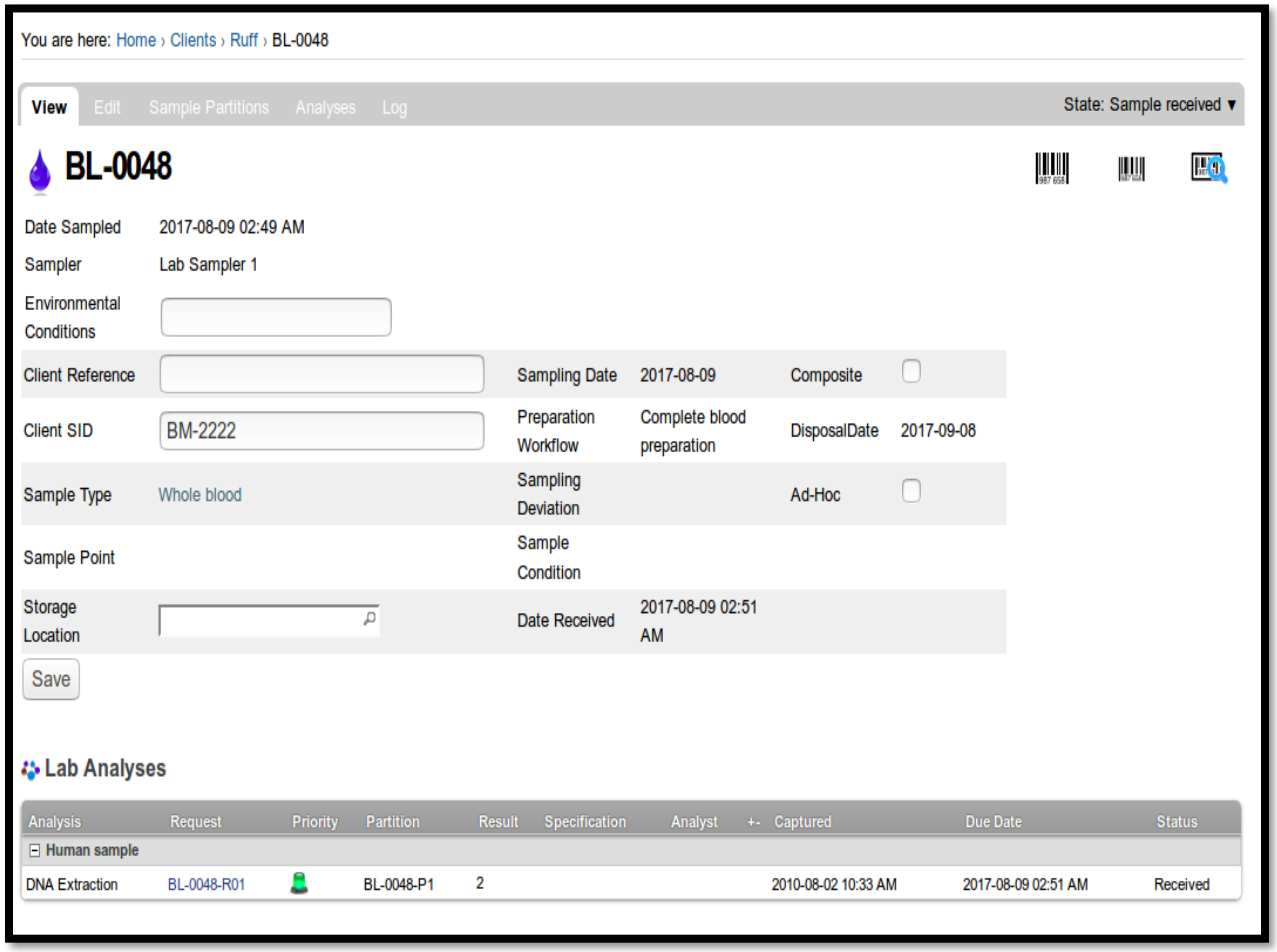




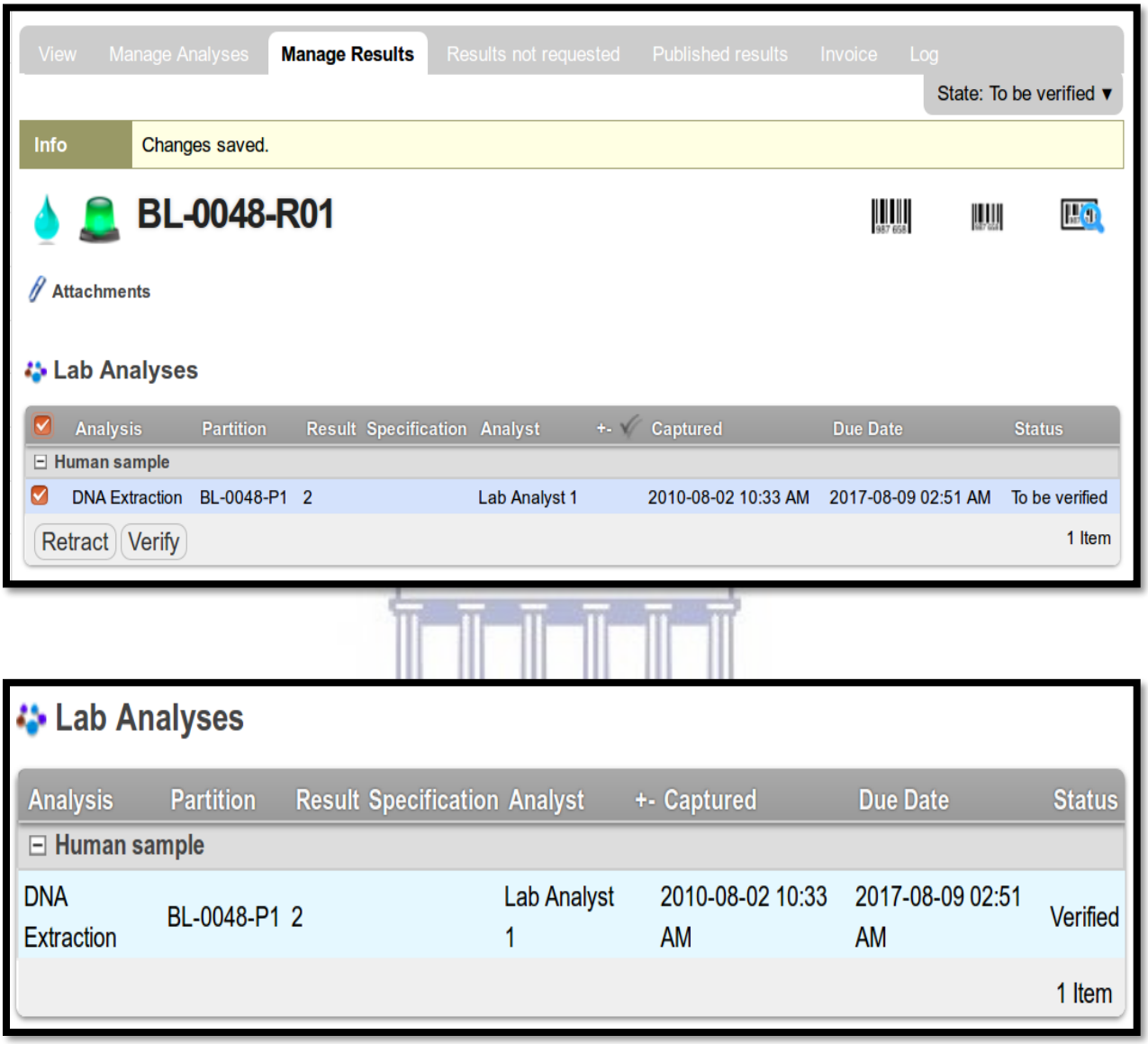
III. “Qubit_03_data.csv” concentration results successfully imported into Bika LIMS.



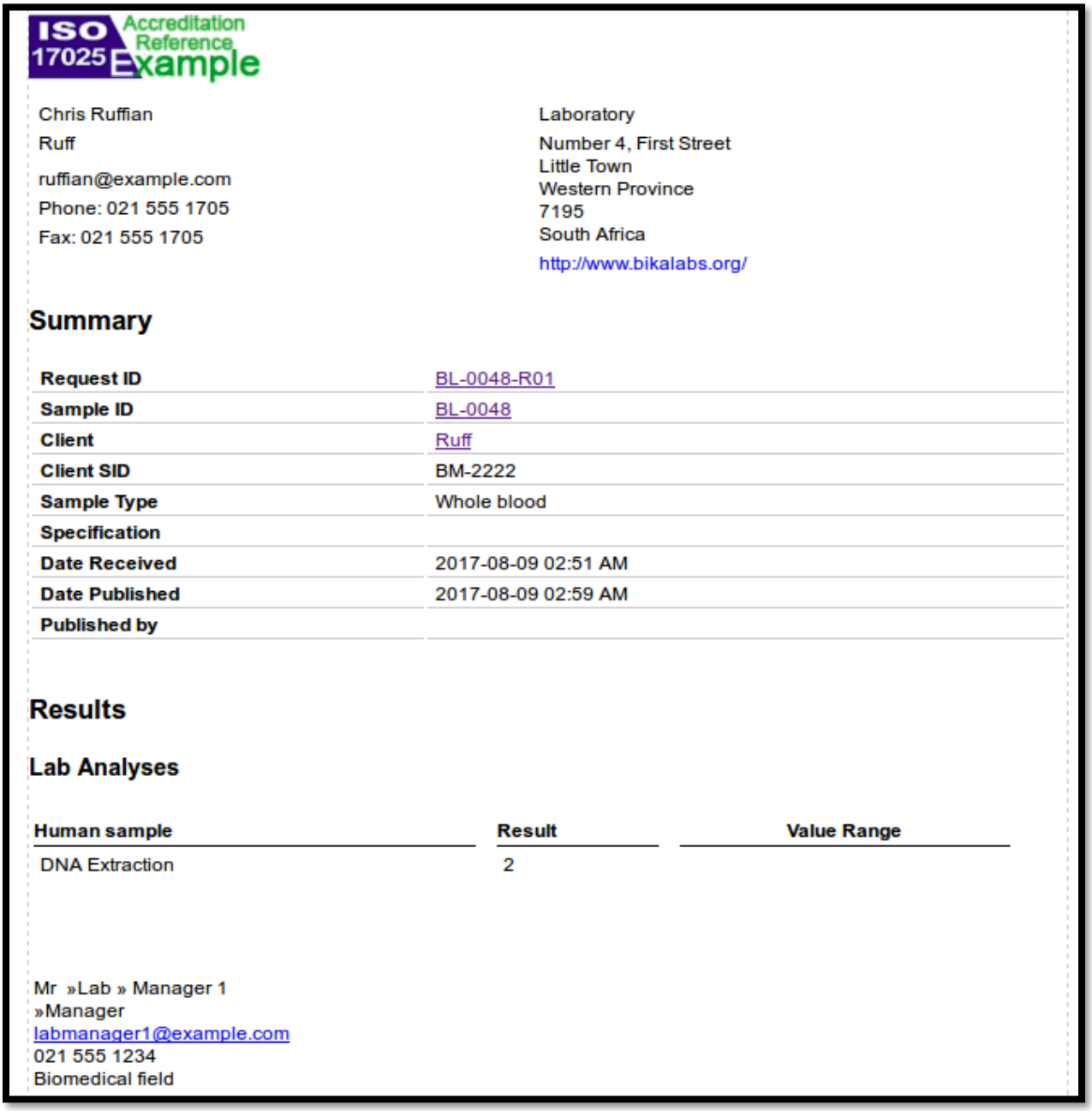
IV. DNA analyses results imported for client sample ID "BM-2222" from "Qubit_03_data.csv" life technology Qubit import interface in Bika LIMS.



V. DNA analysis result imported was selected and verification



VI. DNA concentratiom result for client sample ID “BM-2222” was verified and published.



ISO 17025 Accreditation Reference Example

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Ruff
ruffian@example.com
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Fax: 021 555 1705

Laboratory
Number 4, First Street
Little Town
Western Province
7195
South Africa
http://www.bikalabs.org/

Summary

Request ID	BL-0048-R01
Sample ID	BL-0048
Client	Ruff
Client SID	BM-2222
Sample Type	Whole blood
Specification	
Date Received	2017-08-09 02:51 AM
Date Published	2017-08-09 02:59 AM
Published by	

Results

Lab Analyses

Human sample	Result	Value Range
DNA Extraction	2	

Mr »Lab » Manager 1
»Manager
labmanager1@example.com
021 555 1234
Biomedical field

I. Analysis request for submitted for analyses to be carried out on samples.

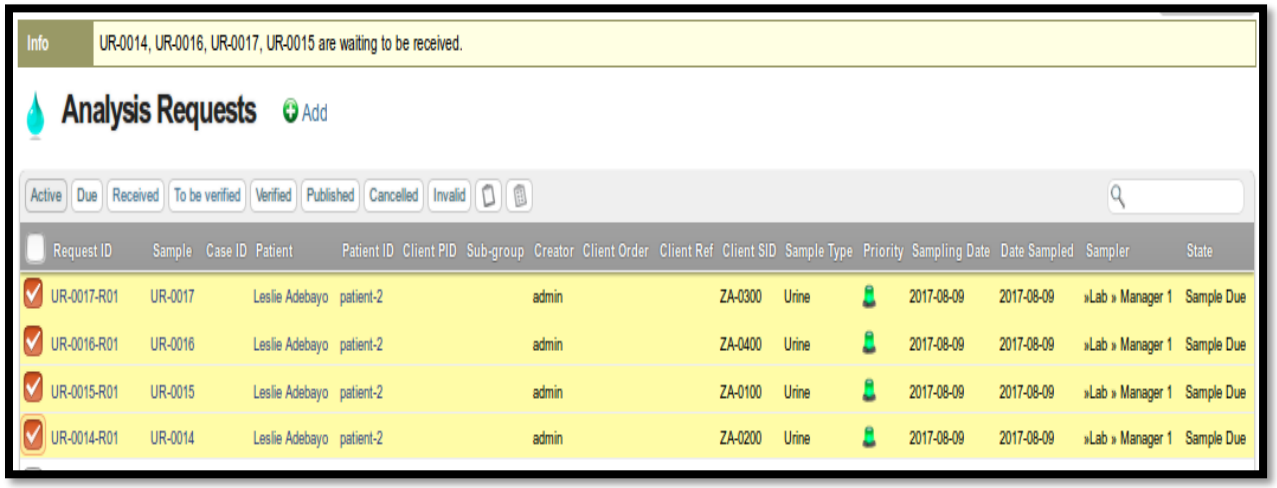
Contact ■	Johanna Smith	Johanna Smith	Johanna Smith	Johanna Smith
CC Contacts				
CC Emails				
Sample *Select a sample to create a secondary AR*				
Case				
Sampling Round				
Sub-group				
Client Patient ID				
Patient ■	Leslie Adebayo	Leslie Adebayo	Leslie Adebayo	Leslie Adebayo
Doctor				
Template				
Analysis Profiles				
Sampling Date ■	2017-08-09	2017-08-09	2017-08-09	2017-08-09
Sample Type ■ *Create a new sample of this type*	Urine	Urine	Urine	Urine
Analysis Specification *Choose default AR specification values*				
Sample Point *Location where sample was taken*				
Storage Location *Location where sample is kept*				
Client Order Number				
Client Reference				
Client Sample ID	ZA-0100	ZA-0200	ZA-0300	ZA-0400

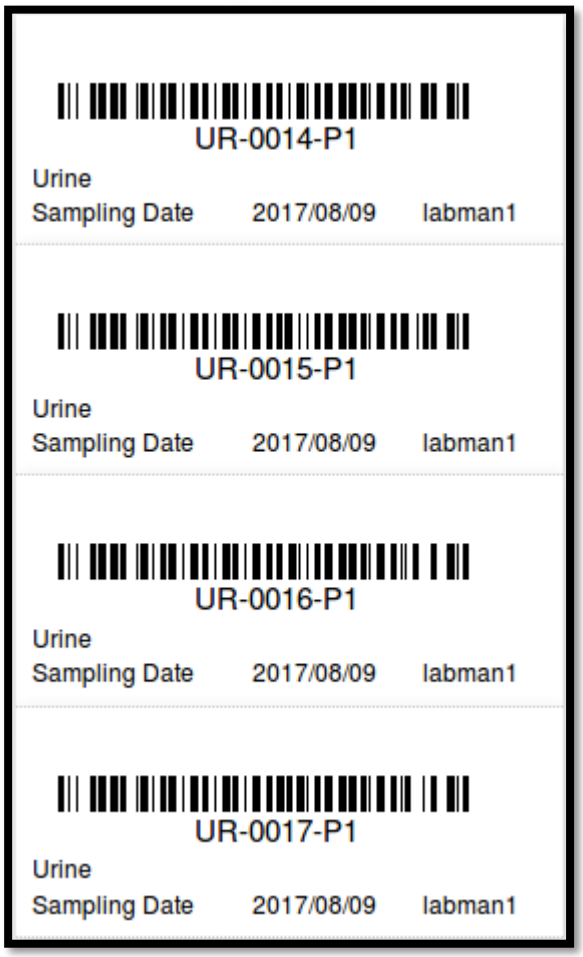
II. Results data “Qubit_04_data.csv” generated from the analytical instrument for RNA

Qubit_04_data.csv

```
Sample Id,Specimen Type,Date,Time,Reading,Unit,Concentration,Unit,Remark
ZA-0100,,2017/08/03,15:03 PM,3.8,ug/ml,33.63,ng/ul,Good sample
ZA-0200,,2017/08/03,15:03 PM,13.84,ug/ml,2.5,ng/ul,Good sample
ZA-0300,,2017/08/03,15:03 PM,27.33,ug/ml,13.65,ng/ul,Good sample
ZA-0400,,2017/08/03,15:03 PM,0.976,ug/ml,21.45,ng/ul,Good sample
```

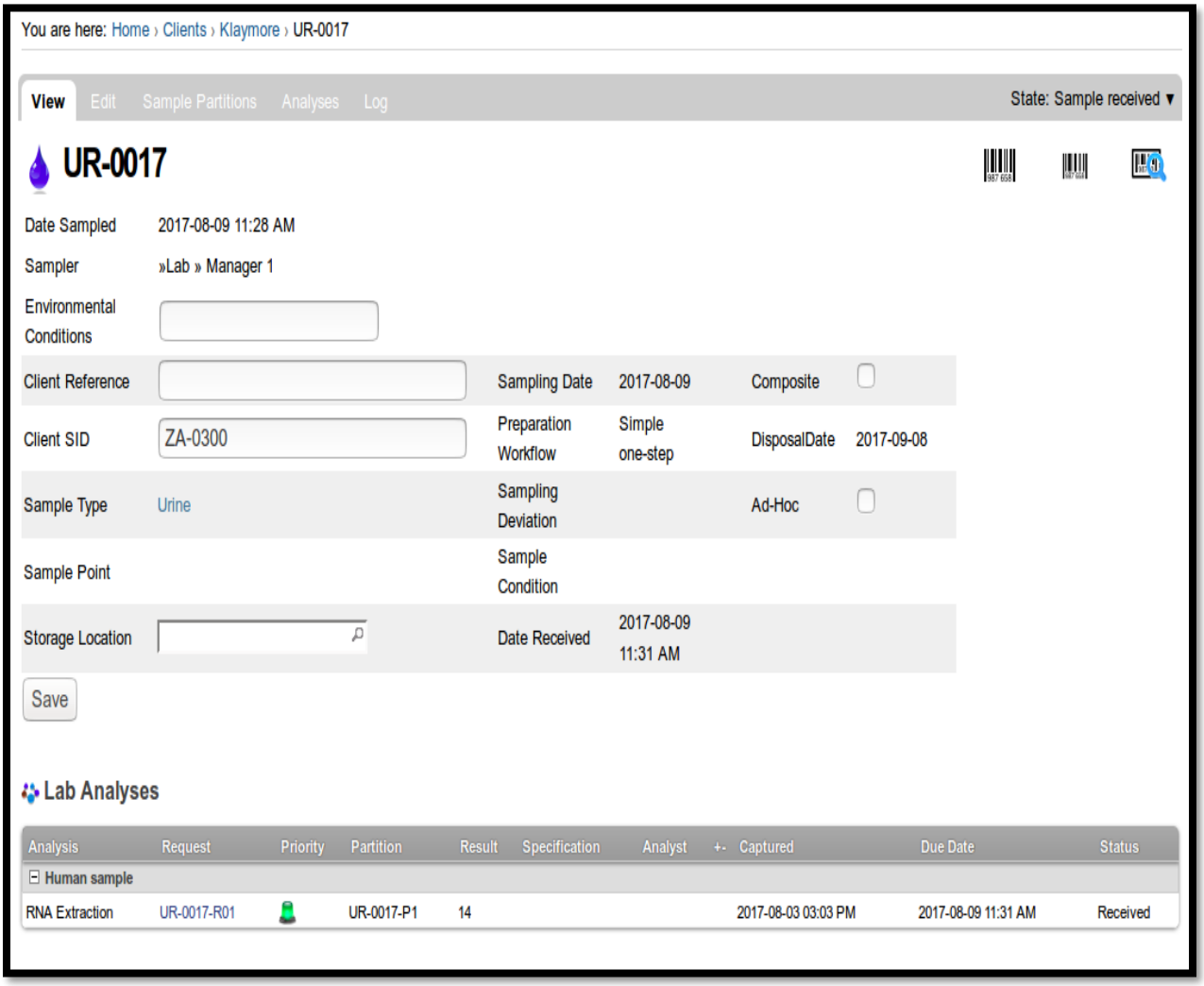
III. Sample received in the laboratory and barcode are generated for the samples.



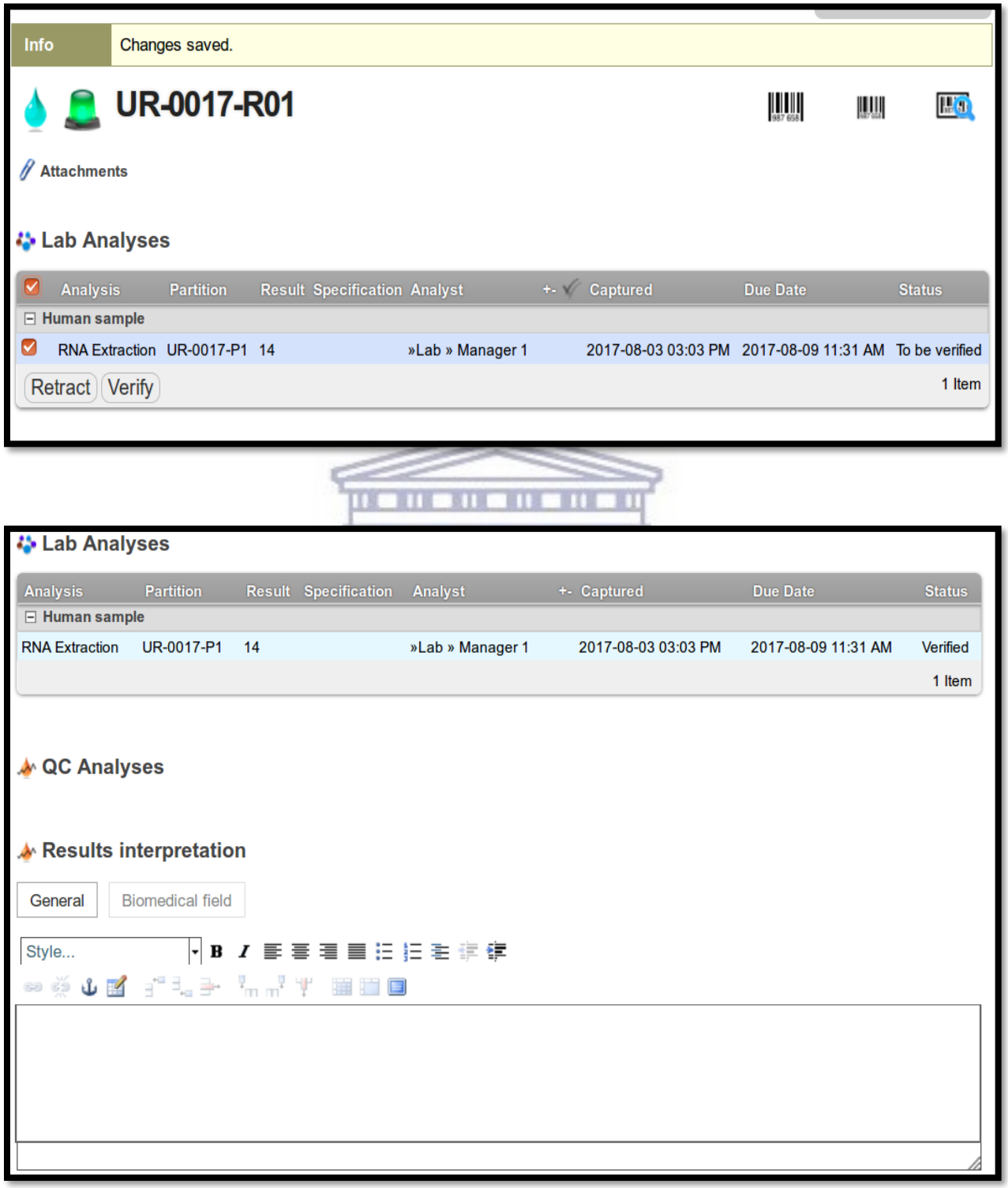


IV. Life technology instrument import interface was selected and RNA concentration results were imported into Bika LIMS by submission of results.

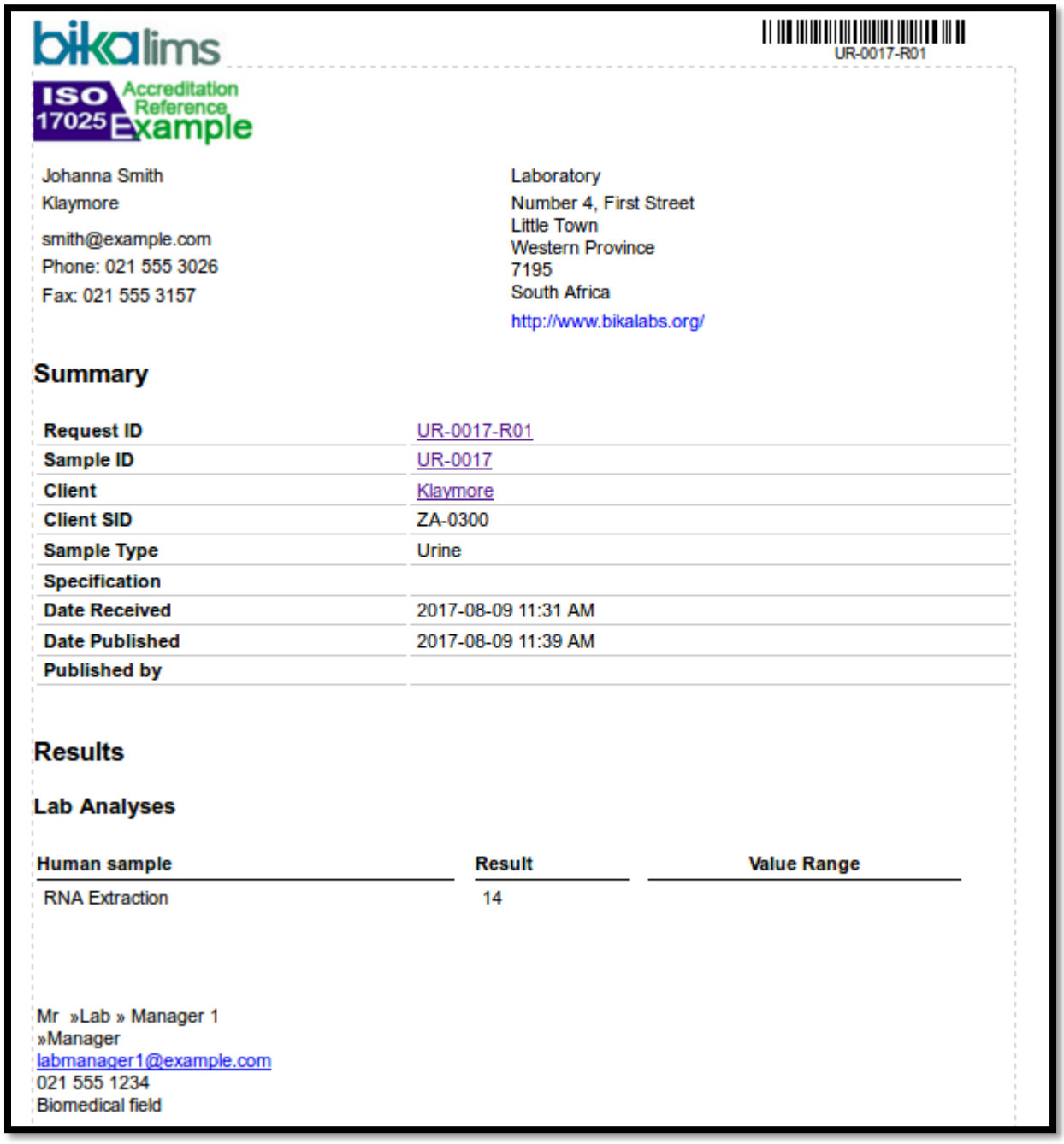
V. DNA analyses results imported for client sample ID “ZA-0300” from “Qubit_04_data.csv” life technology Qubit import interface in Bika LIMS.



VI. DNA analysis result imported was selected and verification



DNA concentratiom result for client sample ID “ZA-0300” was verified and published.



bikalims

UR-0017-R01

ISO 17025 Accreditation Reference Example

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Summary

Request ID	UR-0017-R01
Sample ID	UR-0017
Client	Klaymore
Client SID	ZA-0300
Sample Type	Urine
Specification	
Date Received	2017-08-09 11:31 AM
Date Published	2017-08-09 11:39 AM
Published by	

Results

Lab Analyses

Human sample	Result	Value Range
RNA Extraction	14	

Mr »Lab » Manager 1
»Manager
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Biomedical field