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Department of Industrial and Systems Engineering

BPJ 420 Final Report

Production Planning in the Pharmaceutical Industry to Accommodate the Projected Increase in Tuberculosis

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Acknowledgements

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Executive summary

The report defines the project aim as follows: develop a demand forecast for tuberculosis treatment medicine in South Africa based on mortality and infection rates from 2010 to 2020 and evaluate the current production process and make possible recommendations to meet this demand. The project aim will be achieved by using statistical methods for forecasting and simulation techniques for optimisation.

Production planning represents the master plan to achieve an efficient production system. It incorporates a variety of elements with the purpose of realising accurate delivery times to the customer. With an effective production plan the manufacturing process has the ability to reach its full potential.

In 2009 Sanofi-Aventis was awarded the government contract to be the sole supplier of tuberculosis treatment medication in South Africa. The prevalence of TB in South Africa is undeniably growing when one evaluates the mortality statistics for the last few years and as the HIV infection rate increases so too does the TB rate. It is with this knowledge that one has the responsibility and obligation to provide the people of South Africa with the necessary access to the treatment that is needed to regain health. This reflects the importance of being the sole provider of this potentially life-saving drug. It is therefore imperative that the production of this drug is running at its most efficient level because bottlenecks could not only cost money, it could potentially cost lives.

The demand forecast shows an upward trend from 5 million patients in 2010 to upwards of 7.5 million patients in 2020 with an average growth rate of 300 000 new patients needing treatment every year. The production simulation reveals that the production system is operating under capacity and cannot meet the demand for Rifafour e-275 treatment medication.

Table of Contents

List of Tables and Figures

1. Introduction and background

The pharmaceutical industry is a competitive and ever changing industry with strict guidelines and manufacturing standards. Entry into the market is difficult and keeping a competitive market edge is of high importance for success. Knowing what the target market needs and wants is valuable information but being able to predict what it will need and want is invaluable information. With the combination of population statistics and demand forecasting one can formulate a demand forecast to ensure the delivery of quality product to the clients and the public. Once the forecast is achieved a simulation model will evaluate the production system and possible improvements will be made and tested through the simulation model thus keeping the competitive edge by allowing production to meet demand.

2. Project aim

The project aim consists of two main objectives: develop a demand forecast for tuberculosis treatment medicine in South Africa from 2010 to 2020 based on mortality and infection statistics, evaluate the current production process and make recommendations to meet this forecast demand. The project aim will be achieved by using statistical methods for forecasting demand and simulation techniques for production optimisation.

3. Project scope

The project scope comprises of an investigation into the mortality and infection statistics of tuberculosis patients in South Africa, the development of a demand forecast based on the investigation and a simulation model that mimics the current production process as well as simulation experiments to measures the process capability. The limitations on reliable data define the boundaries of the demand forecast. The statistical data is supplied from medical publications and may be subject to bias as well as poor research and statistical technique and were data was corroborated from different sources, it was used. The production environment poses a limitation to change. Established methods of manufacture inhibit the implementation of possible improvements to the production line, space and resource restrictions also limit the production processes ability to change. And the production process remains in principle the same.

4. Literature review

The objective of the following literature review is to help understand the problems at hand and to gain insight and understanding into the project environment so as to develop solutions that are viable and lasting.

4.1 Forecasting Methodology and Techniques

Put simply demand forecasting is the activity of estimating the amount of product or service that a customer or consumer will need or purchase. A good forecast is based on empirical historic data in order to make educated guesses and quantitative judgement, a forecast however is not 100% accurate. A multitude of forecasting techniques can be used, the methods that will best suite this project will be those based on quantitative data, these methods include: extrapolation, rule based forecasting and segmentation. A methodology tree is a good tool for selecting the appropriate forecasting techniques. (www.forecastingprinciples.com)

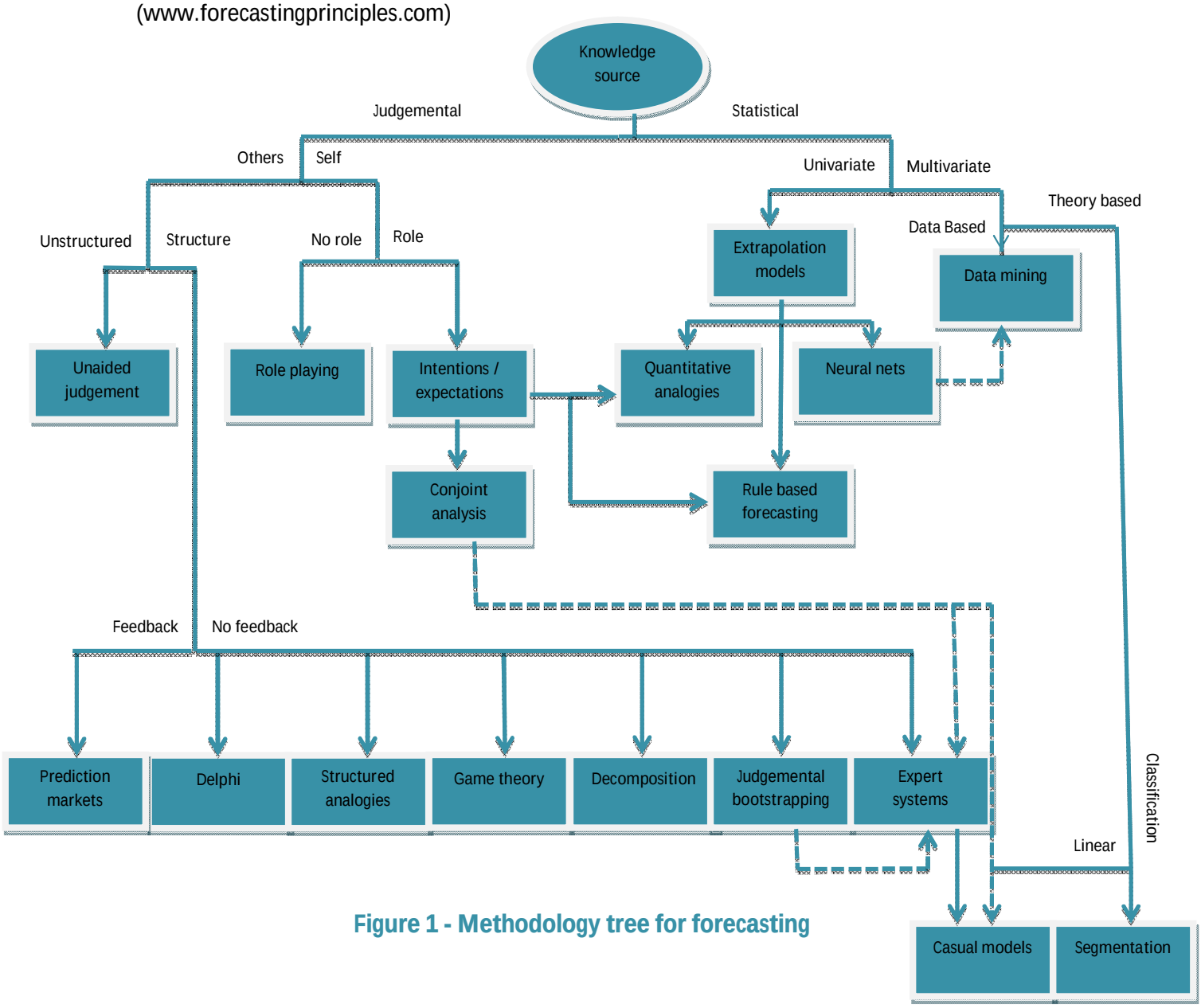

Figure 1 - Methodology tree for forecasting

4.1.1 Relevant forecasting techniques

4.1.1.1 Extrapolation

To extrapolate, one looks at the historical values of a particular data set and based on mathematical methods, predicts where the future data points will be. The different methods of extrapolation include linear extrapolation, polynomial extrapolation, conic extrapolation and French curve extrapolation. French curve extrapolation was used to create a forecast on the growth of HIV/AIDS in the UK (AIDSCJDUK.info Main Index).

4.1.1.2 Rule based forecasting

Essentially rule based forecasting is an extrapolated forecast the trend that has met the prior expectations of a manager, hence a simple rule may be applied. In order to achieve a reliable rule based forecast one must perform statistical analysis, inspection and must have knowledge and insight into the data source (Armstrong, Adya, &Collopy 2001). Knowledge and insight into the data source are the most valuable attributes to rule based forecasting, as well as a strong trend pattern where forecasts are needed for an extended period of the time.

4.1.1.3 Segmentation

Segmentation relies on dividing the problem into its individual segments and using its segments to perform a forecast. The behaviour forecast of the segments are then summed which then gives a total forecast which takes into consideration the variability between the segment forecasts.(Armstrong 1985) says that where there is interaction between variables, the effect of variables on demand are non-linear, and the effects of some variables can dominate others, segmentation has advantages over regression analysis.

4.1.2 Forecast Software

Crystal ball by Oracle is a leading spread-sheet based application and MS excel add-in used for predicting modelling, forecasting, simulation and optimization (http://www.oracle.com). It is used for tactical decision making in uncertain markets. "Crystal Ball is involved in every major investment decision that we make for wells." – Hugh Williamson, Risk and Cost Advisor Drilling and Completions for BP. One of the key benefits of the crystal ball package as defined by BP was to Enabled productive conversations among engineers about likely project outcomes. (Oracle customer case study, BP, 2008).

4.2 Simulating Methodology and Techniques

The optimisation and changes to the current production environment requires the use of a simulation model. The model's aim is to simulate the current production system then make changes within the simulation and test for improvements in speed and efficiency.

4.2.1 The origins of simulation

The origins of simulation modelling stem from the late 1950's, but methods have advanced significantly since the turn of the millennium. The first generation computers were the tools used to explore the field of simulation. With the development of programming language and increased processing power the usefulness increases with technology.

The 1970's marked a period of innovation in the computing world and with it came the leaps in simulation modelling languages such as SLAM and GPSS-H.

The general use of simulation for commercial purposes was extremely limited before the 1980's and only once organizations had access to the powerful computers of the time and simulation software became more user friendly did simulation modelling go main stream.

Present day sees simulation modelling as having been evolved into a recognised technique. This is as a result of the wide use of personal computers and easily available simulation software as well as access to the World Wide Web.

4.2.2 Simulation as an effective tool

The ***advantages*** of using simulation modelling are the following

- Time within the model can be compressed so that years of running in reality can be reduced to mere minutes of elapsed time.
- Changes can be implemented within the model and the effects on the system can be evaluated.
- Testing various alternatives to the system can be done without effecting on-going operations.
- One can represent the modelled system as it looks currently with the use of animation

The ***disadvantages*** of using simulation are the following

- Due to the stochastic nature of the inputs, the outputs may be victim to the same randomness if not properly managed.
- The simulation model is not the answer to all the questions it is an aid in problem solving and decision making.
- The outputs on a complex model are not always easily interpreted.

4.2.3 The different types of simulation models

It is important to understand under which simulation category the problem will fall, there are three main modelling dimensions as defined by (Law & Kelton, 1991:6)

Is the model dynamic or static?

A static model is one where time does not play a role in the evolution of the system. A dynamic model however, is a model that does evolve over time.

Is the model deterministic or stochastic?

When probability plays no role in the system it is considered deterministic. A stochastic model is one where randomness plays an important role within the system.

Is the model continuous or discrete?

A discrete system is one where the state variable is changed at separate instants of time. A continuous model is where the state variable changes continuously with time.

4.2.4 Analysing the system

In order to analyse and model the system one needs to follow certain guidelines or framework in order to ensure a flow through the simulation modelling process and to minimise errors and misconceptions within the model. The appropriate framework for developing a simulation model will be from (Law & Kelton, 1991:107) which breaks the process down into 10 steps namely.

1. Collect data and define model
2. Validate. If not valid go back to step 2, if valid continue to step 3
3. Construct a computer program and verify
4. Make a pilot
5. Formulate the problem and plan the study
6. Validate, if not valid go back to step 2, if valid continue to step 7
7. Design experiments
8. Make production runs
9. Analyse the output
10. Document, present and implement results

4.2.5 Software packages

There are a variety of simulation software packages to choose from such as Automod, Simpak and Arena. They represent the latest generation of simulation software which is commercially available. The majority of them are based on previously developed languages such as SIMAN, Simscript, GPSS and SLAM. The benefits of the latest software packages include; user friendly interface, advanced graphical displays and ever improved assistance files.

The techniques reviewed in the literature will be evaluated and used in section 6.

5. The Project Environment

5.1 What is tuberculosis

Robbins Basic Pathology (8th ed.) defines tuberculosis as a common and often deadly infectious disease caused by various strains of micro bacteria. The disease is most often contained within the patient's lungs but can spread to other parts of the body. It is an airborne disease and can be transferred through coughing, sneezing or through spittle (Konstantinos, A (2010)). Once TB is active and left untreated, it is likely to kill 50% of sufferers. The treatment of TB is prolonged and complex and requires multiple antibiotics. TB is highly contagious and it is believed that one third of the world's population is infected by M. tuberculosis (Jasmer RM, Nahid P, Hopewell PC (December 2002) although could remain dormant in most cases. It has a high infection rate which the world health organization believes is around one person per second.

5.1.1 Treatment

Antibiotic forms the main treatment of TB as it kills the bacteria that causes TB, however treatment is often difficult because the bacteria has become resistant to many antibiotics (Acharya, PV and Goldman DS (1970)). The most commonly used medications are rifampicin and isoniazid and for effective treatment the medication must be taken for extended periods of time often up to 2 years to entirely remove the bacteria from the body. The required amount of treatment is the following. (Rifafour e-275 dosage instructions, sanofi-aventis)

- Patients weighing 28 kg or under
    - 1 tablet per day
    - 7 days a week
    - For 4 months
- Patients weighing between 30 and 37 kg
    - 2 tablets per day
    - 7 days a week
    - For 4 months
- Patients weighing between 38 and 54 kg
    - 3 tablets per day
    - 7 days a week
    - For 4 months
- Patients weighing between 55 and 70 kg
    - 4 tablets per day
    - 7 days a week
    - For 4 months

5.1.2 The Pharmaceutical environment

The pharmaceutical environment adheres to strict rules and guidelines. When performing a study or offering any solutions in such an environment one must be aware of these stringent production practices. A method of GMP (good manufacturing practices) must be followed. GMP's follow these basic principles. (Pharmaceutical Press."Rules and Guidance for Pharmaceutical Manufacturers and Distributors - Edition: 2007")

- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary
- Instructions and procedures are written in clear and unambiguous language
- Operators are trained to carry out and document procedures.
- Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
- Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- The distribution of the drugs minimizes any risk to their quality.
- A system is available for recalling any batch of drug from sale or supply.
- Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

5.2 TB Forecast Investigation

It is known that among those who have tuberculosis and then become HIV positive, the speed of progression from HIV to AIDS and from AIDS to death is more rapid (Badri, *et al*., 2001), and death rates from tuberculosis are also increased (Connolly *et al.,* 1998; Corbett *et al*., 2000).

At the International conference on AIDS in July 2002 a paper was presented by Wennberg, JL. He investigated the relationship of HIV in TB patients in the general population and he created a mathematical model that estimates HIV prevalence in TB patients which successfully estimated the HIV prevalence in Kosovo based on inpatient samples. His study shows that the prevalence of TB and HIV are very closely linked.

The TB mortality data is published by UNAIDS through the software spectrum 3 which presents the epidemic data of a particular country. Supplementary data is provided by the WHO, every year the World Health Organization requests countries' TB control programs to submit data forms electronically for data collection on case notifications, treatment outcomes, implementation of strategy, the financing of TB programs and used to produce

annual assessment of the world's TB status and progress. The data was attained for South Africa from a period of 18 years from 1990 to 2008.(www.who.int)

Table 1 – Summary of TB mortality data (UNAIDS)

Year	No. Mortality
1990	55926
1991	56696
1992	57508
1993	58268
1994	59469
1995	61205
1996	62855
1997	64486
1998	42227
1999	42768
2000	42706
2001	42490
2002	42186
2003	41801
2004	41430
2005	41313
2006	41126
2007	40883
2008	66627
2009	65639
2010	63876

Table 2 - TB/HIV prevalence in South Africa 2002-2008 (www.who.int)

Year	Number of TB patients with known HIV staus
2002	15709
2003	12543
2004	14289
2005	67988
2006	110235
2007	136247
2008	150542

Table 3 - HIV prevalence in South Africa 1990-2008 (www.who.int)

Year	Population	Incedence HIV Positive
1990	36745000	11000
1991	37640000	17000
1992	38591000	25000
1993	39561000	29000
1994	40501000	41000
1995	41375000	54000
1996	42167000	69000
1997	42890000	87000
1998	43562000	110000
1999	44215000	140000
2000	44872000	170000
2001	45536000	210000
2002	46197000	250000
2003	46849000	280000
2004	47477000	300000
2005	48073000	320000
2006	48639000	330000
2007	49173000	330000
2008	49668000	340000

Percentage of deaths in South Africa, 2004 where TB is classified as a certain infections & parasitic disease

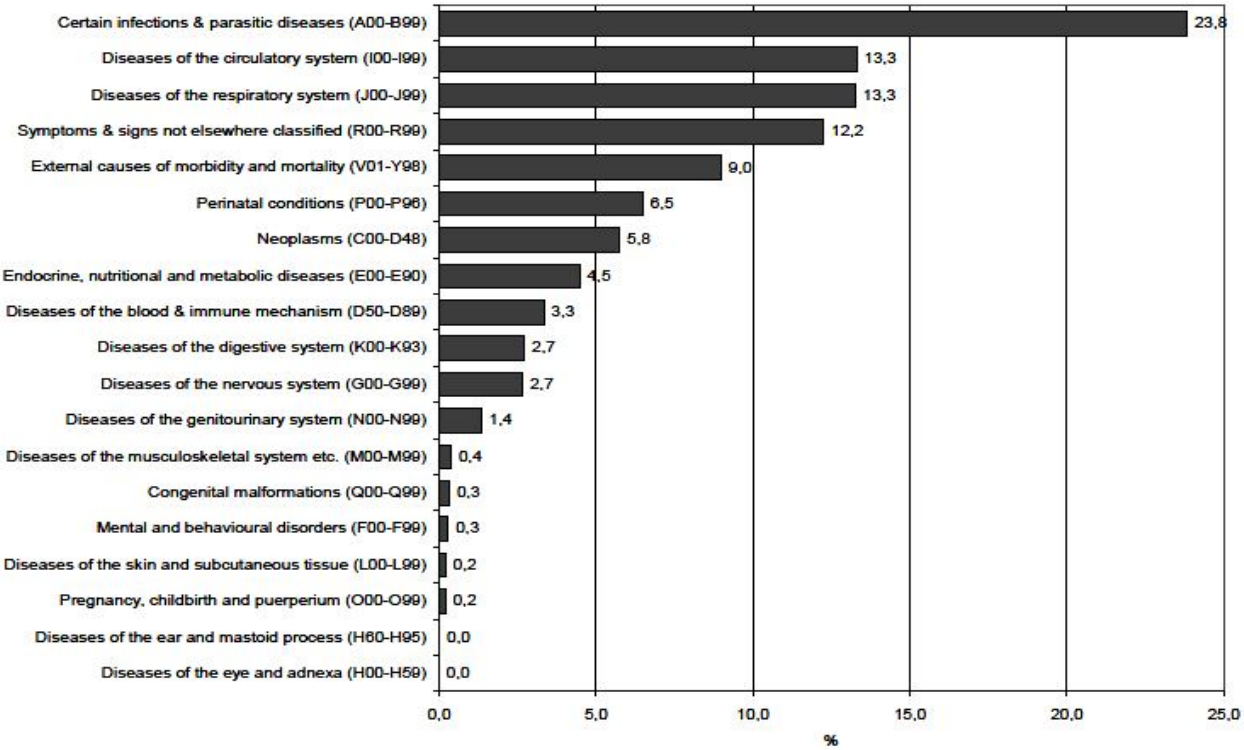

Figure 1 - % of deaths by certain causes in South Africa 2004 (Statistics SA)

Table 4 - Causes of death 2004 & 2005 (Statistics SA)

Causes of death (Based on the Tenth Revision, International Classification of Disease, 1992	Rank	2005		2004*	
		Number	%	Number	%
Tuberculosis (A15–A19)	1	73 903	12,5	70 355	12,3
Influenza and pneumonia (J10–J18)	2	45 596	7,7	45 580	8,0
Intestinal infectious diseases (A00–A09)	3	28 548	4,8	26 740	4,7
Cerebrovascular diseases (I60–I69)	4	24 437	4,1	25 226	4,4
Other forms of heart diseases (I30–I52)	5	23 963	4,1	23 925	4,2
Diabetes mellitus (E10–E14)	6	18 423	3,1	17 071	3,0
Certain disorders involving the immune mechanism (D80–D89)	7	16 171	2,7	16 226	2,8
Chronic lower respiratory diseases (J40–J47)	8	15 738	2,7	15 521	2,7
Respiratory and cardiovascular disorders specific to the perinatal period (P20–P29)	9	15 457	2,6	13 478	2,4
Human immunodeficiency virus [HIV] disease (B20–B24)	10	14 532	2,5	13 440	2,3
Other natural causes		261 317	44,2	251 819	44,0
Non-natural causes		53 128	9,0	52 969	9,3
All causes		**591 213**	**100,0**	**572 350**	**100,0**

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Table 5 - Leading underlying causes of death 1997 - 2001 (Statistics SA)

SHORT NAME FOR THE SUB-GROUP OF CAUSES OF DEATH	ICD-10 CODES	Total sample			1997		1998		1999		2000		2001	
		N	%	Cum %	N	%	N	%	N	%	N	%	N	%
Total	All codes	279,581	100.0		46,941	100.0	54,856	100.0	59,720	100.0	53,247	100.0	64,817	100.0
Unspecified unnatural causes	Y10-Y34	30,728	11.0	11.0	7,164	15.3	7,225	13.2	6,450	10.8	4,591	8.6	5,298	8.2
Ill-defined causes of mortality	R95-R99	22,904	8.2	19.2	4,052	8.6	4,596	8.4	4,449	7.4	4,227	7.9	5,580	8.6
Tuberculosis	A15-A19	22,347	8.0	27.2	3,054	6.5	3,889	7.1	4,557	7.6	4,562	8.6	6,285	9.7
HIV disease	B20-B24	20,679	7.4	34.6	2,170	4.6	3,272	6.0	4,811	8.1	4,802	9.0	5,624	8.7
Influenza and pneumonia	J10-J18	17,672	6.3	40.9	2,126	4.5	2,992	5.5	3,576	6.0	3,856	7.2	5,122	7.9

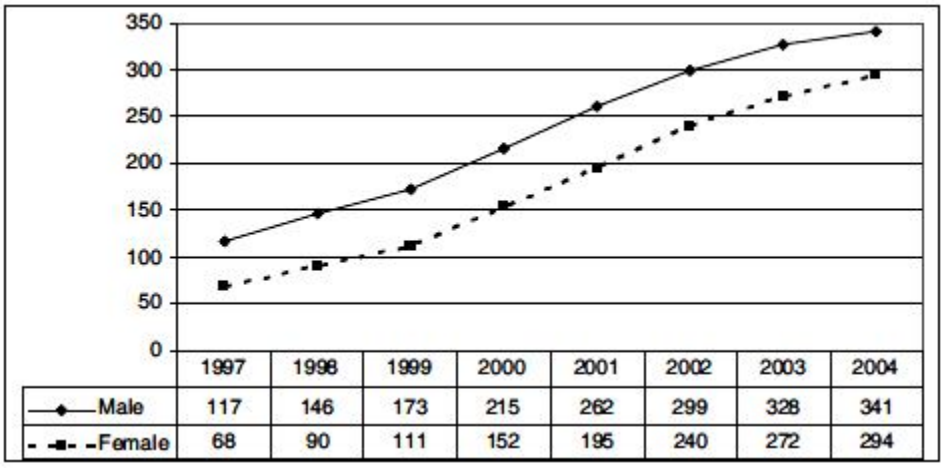


Figure 2 - Age-standardised death rates per 100,000 from tuberculosis by sex (Statistics SA)

As cause of death is a fair indication on disease and infection prevalence the following data is presented from Statistics SA (Mortality and causes of death in South Africa,2005: Findings from death notification)and (Adult mortality (age 15-64) based on death notification data in South Africa: 1997-2004.) as well as (Causes of death in South Africa 1997-2001: Advance release of recorded causes of death (P0309.2)) These publications present data on mortality and causes of death on all notification forms as received by the department of home affairs. One can use the data to validate the different sources further improving the data accuracy.

The data and figures presented show the upward trend of tuberculosis infection and mortality and with the data attained one can select the most appropriate forecasting

technique using the Methodology tree for forecasting (forecastingtechniques.com), see section 4.1, to create a reliable and usable forecast to predict the demand for TB treatment medication. This application is presented in section 7.1.

5.3 Production Process

The production process of the Tuberculosis treatment drug is a delicate one, it comprises of 10 steps, each dependent on the process before it. The production process is very susceptible to variability as many machine and operator times vary. The process is documentation intensive in order to maintain procedure throughout the production steps and this can also halt production. The 10 production steps are as follows.

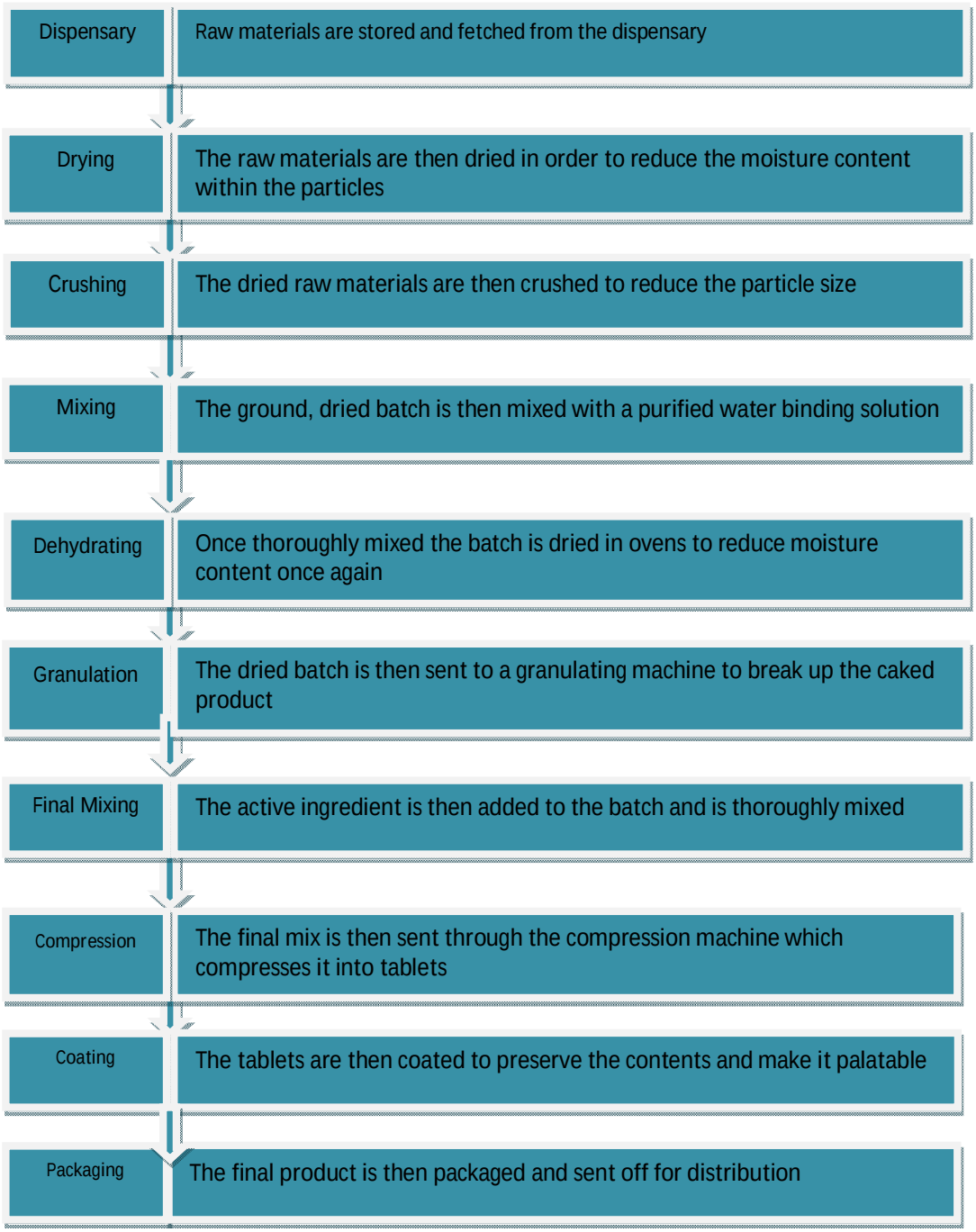


Figure 3 - Production process

5.3.1 Key production features

The production process is both labour and machine intensive. The batch is moved from process to process by an operator pushing a stainless steel trolley, the contents are then loaded into the machine's hopper via scoops or pneumatic hoses. The machines that make up the production plant are unique to their purpose, the current machines in operation in order of sequence are; flatbed dryer, Particle crusher, Solids and liquids mixer, Dehydrating oven, Granulator, Solids Mixer, Tablet compressor, Film coater and packaging machines.

As quality control forms a large part of a pharmaceutical companies operation, the quality control checks are an important part of the system, taking up resources as well as time. The following quality control checks are performed through the production process. Failure of the quality tests results in the batch being run through the machine again costing valuable time and holds the process up significantly.

- QC 1 - Drying

  The batch is tested for LOD % which is loss of dryness once this is in the specified range the batch is then signed of and sent to the next process.

- QC 2 - Crushing

  After the batch is crushed, there needs to be a consistency in particle size, the batch is run in the crushing machine for a certain amount of time at a specific rpm this yields an even spread of the specific particle size which is verified.

- QC 3 - Dehydrating

  After the product has been mixed in the Diason mixer with the purified water solution, the batch is dried in the oven and check for the LOD % and the batch passes it moves onto the next step in the process.

- QC 4 -Granulation

  Once the batch is at the correct dryness, the caked product is broken up and the particle size is further reduced in order for the product to bind properly in the compression process, the particle size is again verified to make sure it is within the specified range.

- QC 5 - Compression

  After the active ingredient is mixed into the batch it is ready for compression, after the compression machine has produced the tablets, a hardness test and a disintegration test is perform to ensure the integrity if the compressed tablet

All these steps in the production process can be represented by a simulation model within the Arena software. And appropriate model is applied in section 7.

6. Selecting the methods for forecasting and simulation

The relevant literature has been reviewed (section 4) and the project environment has been assessed (section 5) hence the reviewed appropriate methods can be applied to the current project environment.

6.1 The TB forecast

The data was attained for the mortality and infection rate for TB is empirical historical data based on investigation performed by both the World Health Organization and Statistics SA. This data will provide a reliable and useful forecast in order to determine the treatment demand trend within South Africa. The forecasting method that will best suite the data source will be determined by following the Methodology tree for forecasting (forecastingprinciples.com).

The characteristics of the data are as follows; statistical and Univariate. This implies, based on the methodology tree, the most appropriate forecasting method is extrapolation models. To further refine and improve the reliability of the forecast, rule based forecasting can be applied by evaluating the forecast result .

The software packages that will be used for the forecast are Microsoft Excel with Crystal Ball add-in an ORACLE product used to make forecasts within excel.

6.2 The Production simulation

6.2.1 Type of simulation domain

The current production environment is generic with regards to line based production, although different in the fact that the whole batch moves from process to process. When deciding what type of simulation model is best suited the environment is compared against the simulation domains as defined by Law & Kelton, (1991:6).

Time is the most important factor within the production process as it ultimately determines the cost and efficiency of the process it thus the system is dynamic as it evolves over time.

Since human and machine involvement is high within the production process, the system will be of a stochastic nature.

The model is termed discrete because changes to the system occur at separate instances of time.

6.2.2 Selecting the appropriate software

The choice of simulation software will be Arena 10. The software package is a product of Rockwell Software Inc. It is an appropriate choice because Arena is user friendly, powerful and familiar to the modeller.

Arena is defined as an event driven simulation software, this means that the model evolves as the events take place on the event list. The event list is a list of all the events that need to be executed in the simulation and they are ranked according to their time of execution. The simulation clock is discrete which means it moves from one event to the other this because the system is only changed once events are executed not as continuous time elapses. The following table shows the list of important elements within Arena that are used to formulate the model (Kelton et al, 2007:20-24).

Table 6 - Important elements in Arena

Concept	Description
Entities	Dynamic objects that change the state of the system, they are created by the create node and destroyed at the dispose node
Attributes	Characteristics of an entity, they attributes can change by using an assign node
Variable	It is a snippet of information that represents a certain characteristic of the system
Resources	A resource captures entities for processing, resources have a seize, delay, release function
Queues	Queues are used to accommodate entities awaiting a resource
Statistical accumulators	These are statistical measures that measure the performance of the output
Events	An instance that happens on the passing of the simulation time
Simulation Clock	Is the current simulation time as it progresses from one event to the next

7. Design of TB Forecast and Production Simulation

7.1 TB Forecast design

7.1.1 Forecast Aim

The aim is to accurately forecast the TB treatment demand for years 2010 to 2020 by using historical data and statistics of TB and HIV infection and mortality as published by the WHO, UNAIDS and StatSA.

7.1.2 Forecast Information

The data gathered is obtained from online resources as publish by the WHO, UNAIDS and StatSA, the data is a reflection of government efforts to monitor epidemics and diseases within the country's borders. Hospital, clinic and death certificate records are used as reference to publish the data.

Figures 5 and 6 are the number of TB and HIV infections every year from 1977 to 2009 as well as the cumulative infections for both TB and HIV. The cumulative infections reflect the number of individuals infected with either TB or HIV within the country.

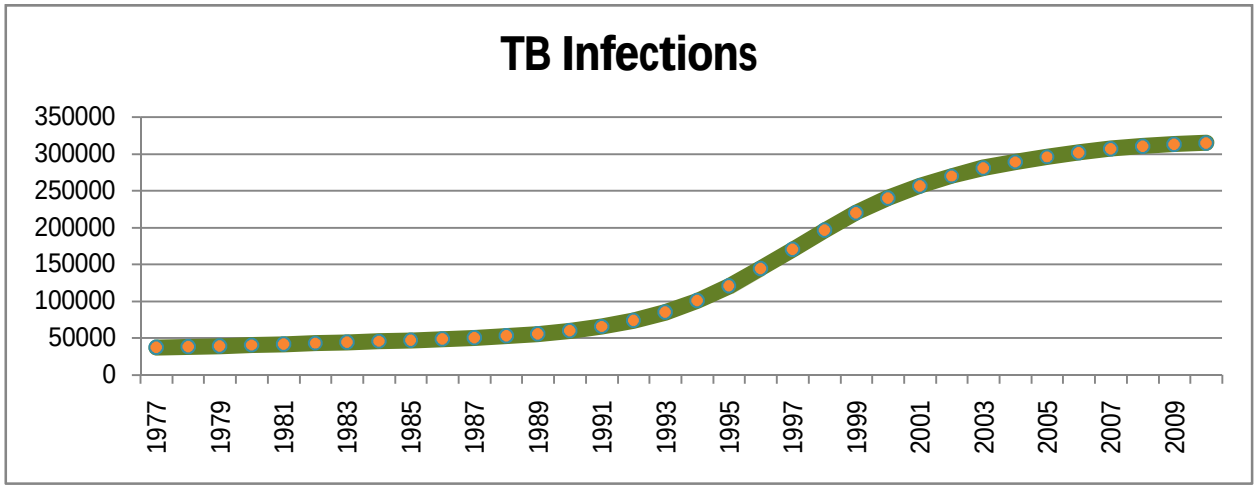


Figure 4 – TB infections per year

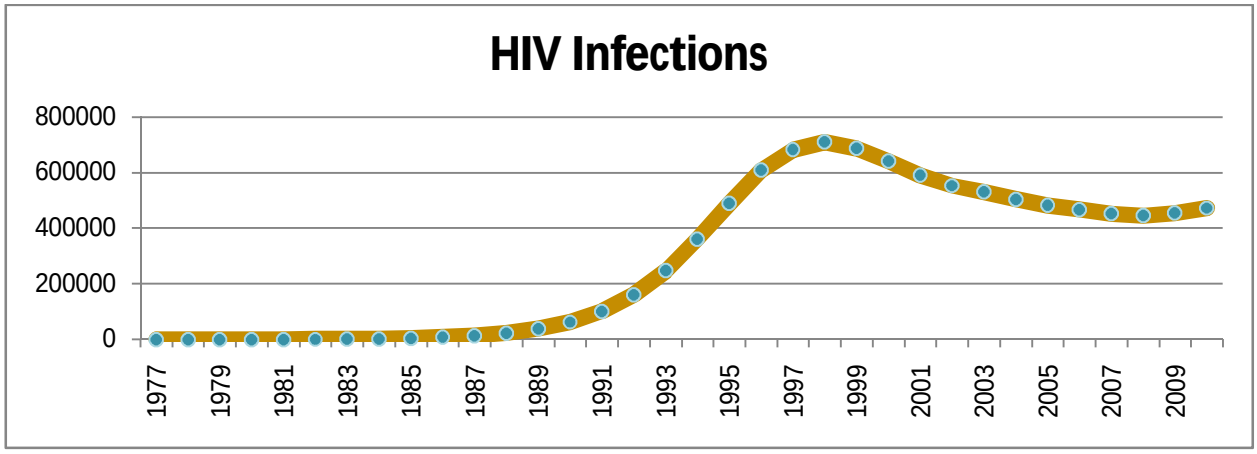


Figure 5 – HIV infections per year

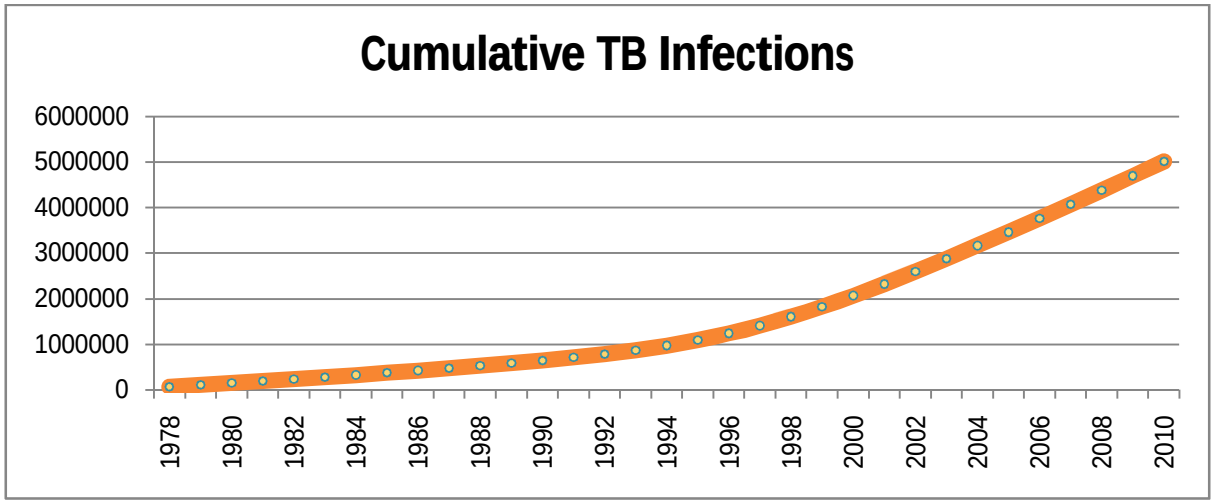


Figure 6 – Cumulative TB infections

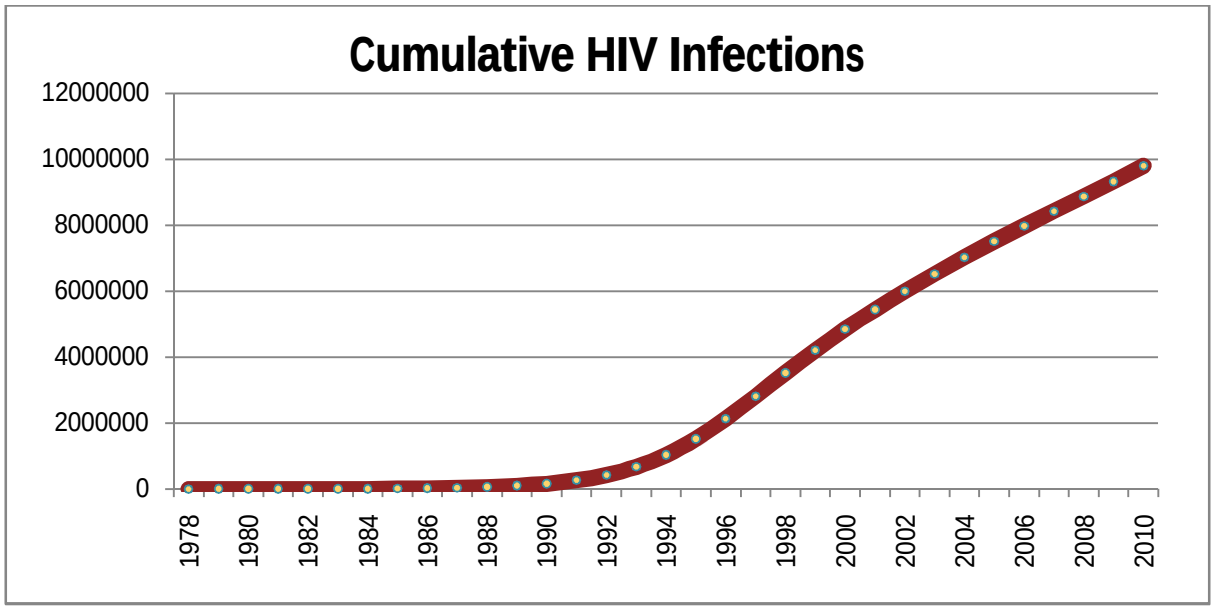


Figure 7 – Cumulative HIV infections

In the Wenneberg, J L paper presented at the international conference for aids in July 2002, he concluded in the paper concluded that there is good agreement between the mathematical model and historical experimental data for the relationship between HIV prevalence in TB patients and the general population. While further confirmation is required, this can be an effective tool for estimating HIV prevalence for healthcare resource allocation particularly in resource poor areas. (Wenneberg, JL, 2002)

Viewing the graphs it can be seen that the link between the HIV and TB infection rates is highly probable. As the study of HIV and AIDS is well resourced and is needed to be accurate it can used to validate the accuracy of the TB infection trend.

7.1.3 Forecasting Method

The demand for treatment is defined by the number of people actively seeking treatment and is the total number of infected patients less the number who have since died from the illness, less those cured by the treatment less, patients that have died from other illness caused by HIV/AIDS which made up the percentage of TB sufferers. This demand is defined by the following equation.

$$D_{TB(x)} = \sum_{1}^{x-1} I_{TB} \quad - \left(M_{TB(x-1)} + C_{TB(x-1)} + TB_{HIV(x-1)}\right)$$

Equation 1 – TB treatment medication demand

Where $D_{TB(x)}$ is the demand for the current year (x)

$\sum_{1}^{x-1} I_{TB}$ is the number of current TB infections (x-1)

$M_{TB(x-1)}$ is the number of TB mortalities the previous year (x-1)

$C_{TB(x-1)}$ is the number of TB patients not needing retreatment the previous year (x-1)

$TB_{HIV(x-1)}$ is the number of TB patients that died from other related diseases caused by HIV/AIDS

The variables defined above form the basis of the forecast where the fundamental variables such as the number of infections make up the highest weight of the forecast as opposed to the other variables which normalize the data in order to reflect reality as best as possible.

7.1.4 Forecast Data Analysis

- TB Infections per year I_{TB}

Table 7 – TB infections per year (UNAIDS)

Year	No. Infect.	Year	No. Infect.	Year	No. Infect.	Year	No. Infect.
1977	37653	1987	50982	1997	170746	2007	307120
1978	38644	1988	53282	1998	196617	2008	310557
1979	39690	1989	56268	1999	220212	2009	313068
1980	40803	1990	60358	2000	240430	2010	315145
1981	42080	1991	66038	2001	256942		
1982	43387	1992	74111	2002	270346		
1983	44708	1993	85479	2003	281187		
1984	46053	1994	100993	2004	289455		
1985	47449	1995	121002	2005	296277		
1986	49097	1996	144955	2006	302204		

The data is obtained from UNAIDS and verified against the WHO report on TB prevalence in South Africa. The trend is seen in Figure 1. Where there is a marked increase in the TB infection rate from 1993 onwards and it is seen to decrease and almost plateau from 2007 onwards. The key changes in the infections rates, exponential increase and plateau, the exponential can be attributed to the wide spread of HIV through the world and country and

the fact that TB infection has a close linked relationship with HIV and the plateau can be attributed to the availability and government sponsorship of anti-retro viral medication as well as the government sponsorship of TB treatment medication.

- TB Mortalities $M_{TB(x-1)}$

The data was analysed from the publication of the WHO on the TB incidence, notification and cases in South Africa. The data exhibits inconsistencies in years 1995, 1999 to 2001 and again from 2007 onwards, the data is obtained from national records of mortality causes based on the cause of death as described by the death certificate, it is by this fact that the data is inconsistent as the cause of death is subject to correct diagnosis, correct disease classification as well as correct record keeping. The variations in the later years can be attributed to the reclassification of diseases where previously one could not state that the patient died as a result of HIV/AIDS, one can now do so.

Table 8 – TB mortalities (StatSA)

Year	No. Deaths
1997	18500
1998	23600
1999	28400
2000	36700
2001	45700
2002	53900
2003	60000
2004	63500

The above data is obtained from a StatSA publication (Adult mortality (age 15-64) based on death notification data in South Africa: 1997-2004) is in conflict with the data as presented by the WHO, where the cause of death is also obtained from death certificates.

Table 9 – TB mortalities UNAIDS

Year	No. Mortality	Year	No. Mortality	Year	No. Mortality	Year	No. Mortality
1977	77032	**1987**	70115	**1997**	64486	**2007**	40883
1978	77177	**1988**	69202	**1998**	42227	**2008**	66627
1979	76767	**1989**	69141	**1999**	42768	**2009**	65639
1980	75766	**1990**	55926	**2000**	42706	**2010**	63876
1981	74947	**1991**	56696	**2001**	42490		
1982	74163	**1992**	57508	**2002**	42186		
1983	73250	**1993**	58268	**2003**	41801		
1984	72462	**1994**	59469	**2004**	41430		
1985	71761	**1995**	61205	**2005**	41313		
1986	70999	**1996**	62855	**2006**	41126		

The above data is published by UNAIDS through the software spectrum 3 which presents the epidemic data of a particular country in a structured easy to use manner, the data represents the number of deaths caused by TB in South Africa. It represent the most complete and consistent data

- Successful TB treatments $C_{TB(x-1)}$

Table 10 – Successful treatments (Department of Health)

Year	Cure Rate %	No. Infect.	No. Cured
1996	53.9	144955	78131
1997	56.6	170746	96642
1998	59.8	196617	117577
1999	60.3	220212	132788
2000	53.8	240430	129351
2001	49.7	256942	127700
2002	50	270346	135173
2003	50.9	281187	143124
2004	50.8	289455	147043
2005	57.7	296277	170952

The above treatment data was obtained from the department of health's (TUBERCULOSIS STRATEGIC PLAN FOR SOUTH AFRICA, 2007-2011) where the cure percentage is measured from the testing of TB patients receiving treatment being retested after treatment.

- TB patient mortalities from other related diseases caused by HIV/AIDS $TB_{HIV(x-1)}$

As this is a difficult statistic to obtain it can be ascertained that the mortality of TB patients from other diseases caused by HIV is the percentage of patients infected with both HIV and TB divided by the total number of HIV infections, multiplied by the total AIDS related mortalities for that year. This is defined by the following equation.

$$TB_{HIV} = (HIV_{TB}/HIV_{tot}) \times AIDS_{Mortality}$$

Equation 2 – TB patient mortalities from other related diseases caused by HIV/AIDS

Table 11 - TB patient mortalities from other related diseases caused by HIV/AIDS

Year	HIV/TB Patients	HIV infections	AID Mortality	TB/HIV Mortality
2002	1798	552635	242401	789
2003	4414	530043	284155	2366
2004	10185	503944	321245	6493
2005	35299	481920	337059	24688
2006	58249	466871	344902	43032
2007	87764	451939	354292	68802
2008	89950	445122	369454	74659

7.1.5 Forecast Evaluation

To evaluate the forecast at hand we need to solve equation 1 which is defined as

$$D_{TB(x)} = \sum_{1}^{x-1} I_{TB} \quad - \left(M_{TB(x-1)} + C_{TB(x-1)} + TB_{HIV(x-1)}\right)$$

To solve this equation assumptions are necessary. For the years where data is not available it is required to extrapolate within a certain confidence interval as for the accuracy of the data it can be assumed that as the data was presented in the form of a formal publication it is accurate.

Table 12 - Demand from 2003 to 2010 based on equation 1

Year	Demand	Tot. Infected Pop.	No. new Infections	TB mortality	No. Cured	HIV/TB mortality *
2003	2702066	2879512	281187	41801	143124	828
2004	2983214	3168967	289455	41430	147043	4610
2005	3272161	3465244	296277	41313	170952	12838
2006	3542345	3767448	302204	41126	151102	22807
2007	3859533	4074568	307120	40883	153560	44033
2008	4146649	4385125	310557	66627	155279	44795
2009	4431492	4698193	313068	65639	156534	60124
2010	4731041	5013338	315145	63876	157573	70605

* Data fitted to trend line and relevant empirical values extrapolated

7.1.6 Forecast Results

Report for Demand Forecast

Summary:

Number of series: 1
Periods to forecast: 10
Seasonality: none
Error Measure: RMSE

Series: Demand **Range:**
2010-2020

Method: Double Moving Average
Parameters:
Periods: 2
Error: 20315

Series Statistics:
Mean: 3708563
Std. Dev.: 711140
Minimum: 2702066
Maximum: 4731041
Ljung-Box: 4.4786

Table 13 - Forecast from 2011 to 2020 (crystal ball)

Date	Lower: 5%	Forecast	Upper: 95%
2011	4983739	5019560	5055381
2012		5311756	
2013		5603952	
2014		5896148	
2015		6188344	
2016		6480539	
2017		6772735	
2018		7064931	
2019		7357127	
2020		7649323	

Table 14 - Method statistics (crystal ball)

	Table Items								
Methods	**Rank**	**RMSE**	**MAD**	**MAPE**	**Durbin-Watson**	**Theil's U**	**Periods**	**Alpha**	**Beta**
Double Exponential Smoothing	2	25024	20287	0.518	3.213	0.086		0.999	0.999
Double Moving Average	1	20315	17771	0.436	2.522	0.071	2		
Single Exponential Smoothing	4	290431	290101	7.69	0.006	1.001		0.999	
Single Moving Average	3	290183	289853	7.683	0.006	1	1		

7.1.7 Number of Patients needing treantment

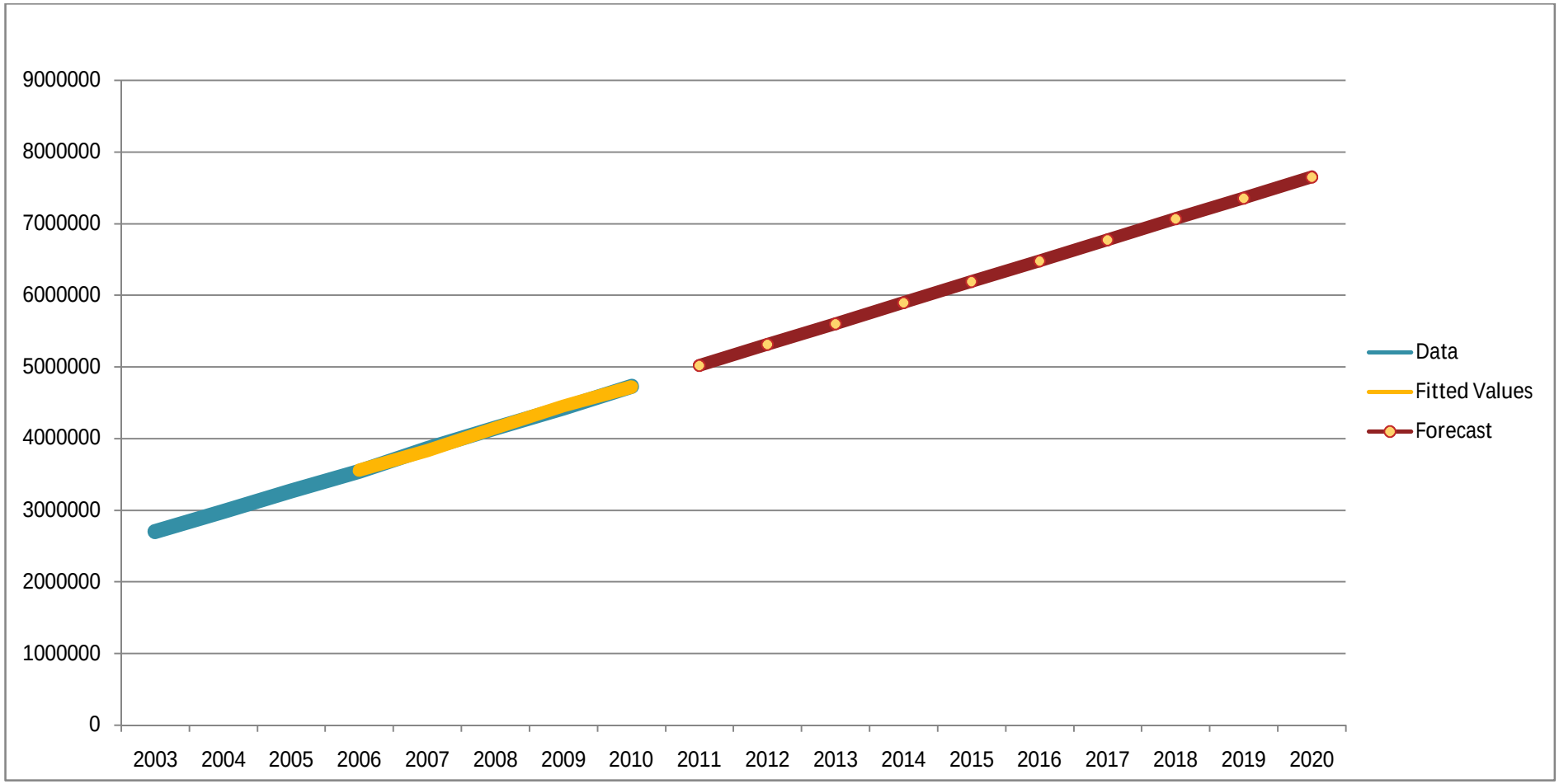


Figure 8 – Patient treatment demand forecast

The figure presented above represents the number of patients requiring treatment from years 2002 to 2020. The demand increases linearly which implies that the rate is constant and that efforts to curb the increase in TB mortalities are stopping the epidemic from increasing exponentially, but it also implies that to keep the rate constant or even decrease, more efforts are needed to truly have the TB epidemic under control.

7.1.6 Medication demand count

To translate the number of patients needing treatments into a treatment medication count the dosage instructions as well as patient category spread. The dosage is defined in section 5.1.1 and the patient category spread is supplied by the Department of Health's TB treatment records. The patient category spread is the following

Table 15 - Weight distribution and treatment requirement

Weight (kg)	Percent of total patients	Total Tablets for treatment course
weight < 30	9	112
30 < weight < 37	33	224
38 < weight < 54	24	336
55 < weight < 70	34	448

Table 16 - Total patients in each weight category

	Number of Patients in weight category			
Date	weight < 30	30 < weight < 37	38 < weight < 54	55 < weight < 70
2011	451760	1656455	1204694	1706650
2012	478058	1752879	1274821	1805997
2013	504356	1849304	1344948	1905344
2014	530653	1945729	1415076	2004690
2015	556951	2042154	1485203	2104037
2016	583249	2138578	1555329	2203383
2017	609546	2235003	1625456	2302730
2018	635844	2331427	1695583	2402077
2019	662141	2427852	1765710	2501423
2020	688439	2524277	1835838	2600770

Table 17 - Required amount of Tablets for forecast

Required amount of Tablets in millions					
Date	weight < 30	30 < weight < 37	38 < weight < 54	55 < weight < 70	Total
2011	51	371	405	765	1 591.00
2012	54	393	428	809	1 683.61
2013	56	414	452	854	1 776.23
2014	59	436	475	898	1 868.84
2015	62	457	499	943	1 961.46
2016	65	479	523	987	2 054.07
2017	68	501	546	1032	2 146.69
2018	71	522	570	1076	2 239.30
2019	74	544	593	1121	2 331.91
2020	77	565	617	1165	2 424.53

The values presented in the above table represent the forecast for the demand of pills from year 2011 to 2020. The forecast tablet demand is the value that the current production processes performance will be measured.

7.1.7 Forecast Conclusion

The investigation into the TB mortality and infection statistics yielded startling trends which were closely linked to the HIV infection statistics, this trend represents the growing number of people suffering from the often deadly infection that need treatment in order to live a good life and contribute to the development of South Africa. The demand for TB treatment saw a marked increase when the HIV infection rates began to increase exponentially, with the introduction of anti-retro viral treatment and awareness campaigns the infection rate began to slow down, eventually reaching plateau then slightly decreasing but still remaining high from 2000 onward.

As a result of these high infection rates the number of people living with TB is constantly on the rise and the number of patients needing treatment is equally on the rise. The forecast yields results that follow the trend from the year 2003 to 2010 showing a linear upward trend with a gradient of just under 300 000 new patients requiring treatment every year. Following this forecast it is clear that in order to meet current demand and future demand the current production process needs to supply treatment for 5 million patients in 2010 and upwards of 7.5 million patients in 2020. The dosage recommendation equates to an average of 400 pills per person per treatment run therefore treatment demand will increase from 1590 million tablets in 2010 to 2400 million tablets in 2020 subject to every person receiving treatment with the correct dosage for the allocated period of time.

7.2 Production Simulation

7.2.1 Production Simulation Aims

The aim of the simulation is to reliably model the complex and dynamic process of producing TB treatment medication for the purpose of analysis and improvement in order to meet the current and future demands for TB treatment medication.

7.2.2 Production Simulation Objectives and Issues

The main objective of the project is to produce a simulation model that reliably emulates the current production process where changes can be made to the simulation model and possible improvements can be validated and tested.

The following issues are important for the Production model

1. Can the current production process meet demand?
2. How is the product throughput affected by changes in the process elements?
3. Are there adequate machines and resources available?
4. Are there adequate machine operators available?
5. Can the production process handle the increase in demand

7.2.3 Production Simulation analysis

Applying the framework as defined by (Law & Kelton, 1991:107) we follow the 10 steps.

7.2.3.1 Step 1 Collect data and define model

The production process elements are mutually dependent because each process is dependent on the one before it finishing before the current process can begin work on the batch, this poses the problem of delays and bottlenecks upstream that effect the throughput of the process. One batch is equivalent to 300 000 tablets. The aid of process flow diagram, a map of the processes will highlight possible problem areas and will help in developing a reliable model.

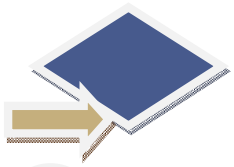
Process flow diagram Elements

Process Element

Resource Element

Parameters Subject to

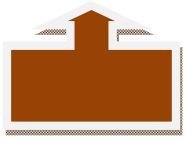
Quality Control Test



Pass

Fail

Add Ingredient



Proceed

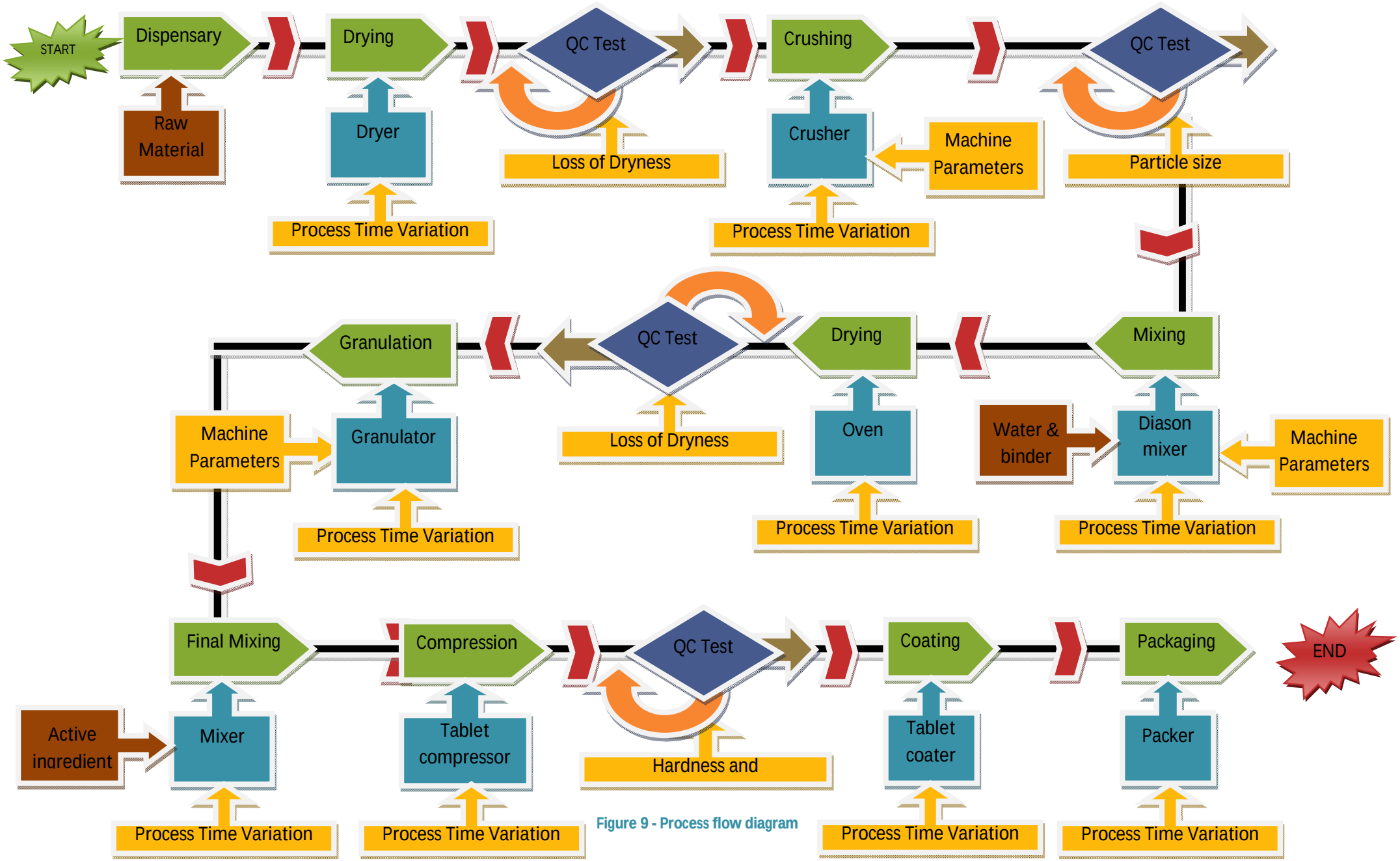


Figure 9 - Process flow diagram

7.2.3.1.1 Data Collection

The data is obtained from the batch manufacturing record's which documents the production process from start to finish, start times and end times of the different processes are readily available within the batch manufacturing records. A total of ten batches were analysed and a summary of the records are as follows.

Resources

Table 18 - Resources in production

Resource name	No
Lightnin Mixer	2
Diosna P600 mixer	1
Alexander No. 2	1
Drying Ovens	3
Bin Blender	1
Compression machine	1
Coater, PACCO 60	1

Average Process Times

Table 19 - Production process average times

Process	Time
Granulation	10 min
Wet granulation	5 min
Drying	11 hrs
Crushing	5 1/2 hrs
Final Mix	4 hrs
Set up for compression	20 min
Compression	7 hrs
Yield Measurement 1	25 min
Mix Coating ingredients	30 min
Coating	6 hrs
Yield Measurement 2	30 mins
Total	35 1/2 hrs

A detailed table of input data with the respective probability distributions are available in appendix A

7.2.3.3.2 Model Definition and Construction Approach

The first step to defining the simulation model is to have an accurate idea how the entity or batch, flows through the resources for example machines and operators. Once the flow has been laid out it is necessary to find out the rate at which the resource may process the entity. This is done via investigation or historical data, because the processing times vary and exhibit a stochastic nature it is necessary to find out the probability distributions of the processing rates and using the distributions within Arena one can input the probable rates into the resource attributes.

7.2.3.2 Step 2 Validate

The system is a line production so therefore a resource only receives the entity once the previous resource has completed it's seize, delay and release.

With regards to the project environment, the simulation role players are defined as the following Arena elements.

Create node – Represent the raw material dispensary where the batch is first introduced into the system.

Entity - The batch of material that moves through the process.

Resources - The machines and technicians that perform the work.

Process – The production process where the resource processes the entity

Attributes – Represents the change in batch properties as it is processed by the resources.

Dispose node – The final point where the process batch exist the system for packaging.

7.2.3.3 Step 3 Construct a computer program and verify

7.2.3.3.1 Assumptions

The following assumption will have to be made in the construction of the model

1. All employees will operate the machines with no absenteeism and stoppage during the shift
2. 1 Day consists of three 8 hour shifts = 24 hours
3. No machine breakdowns will occur
4. No outside means of stoppages will occur i.e. load shedding, employee strike
5. No stock outs or lead times for raw materials and ingredients will occur

7.2.3.4 Step 4 Make a pilot

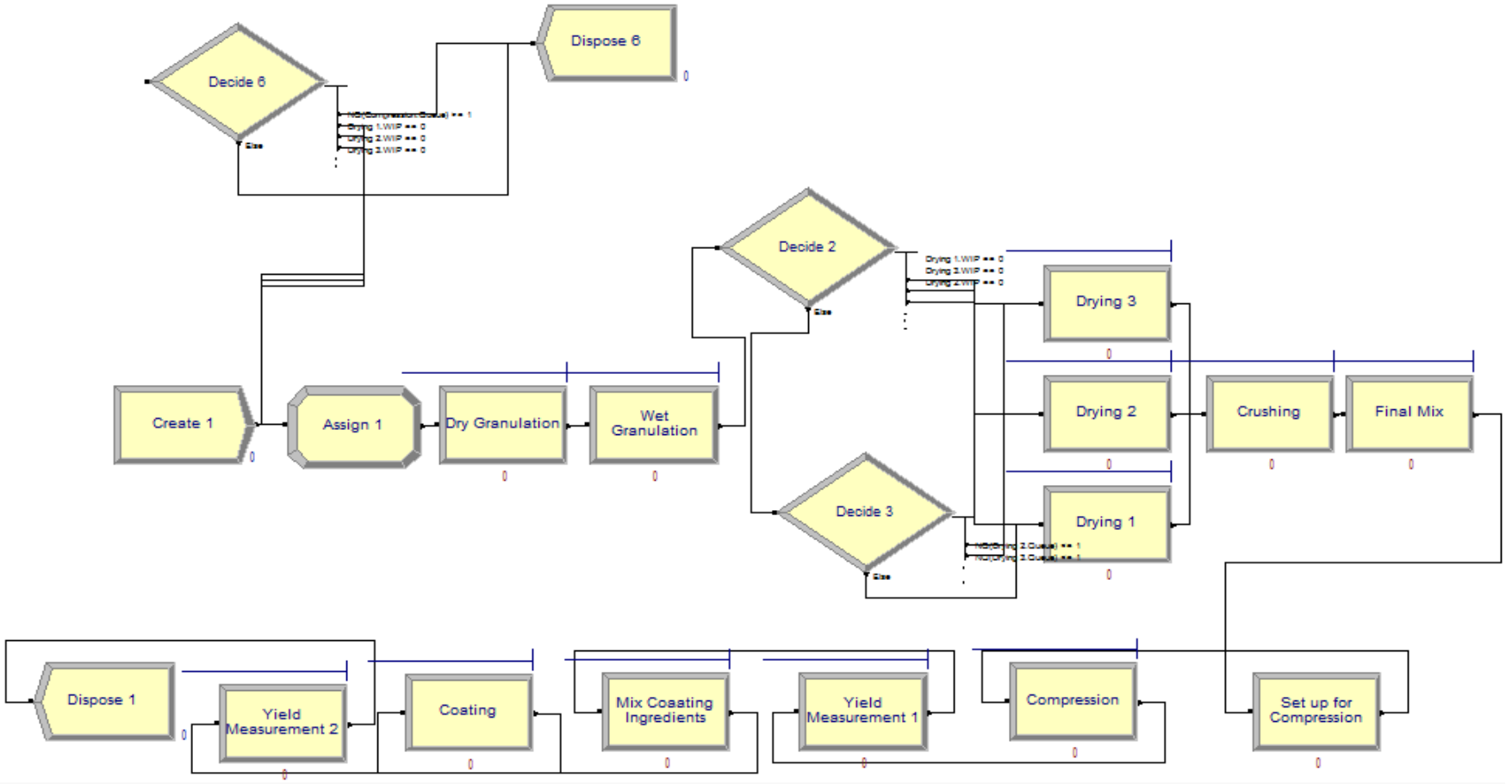


Figure 10 - Arena Pilot model

The pilot model is representative of the production process in reality, the description of entity flow through the model is as follows: the create node creates an entity every 10 hours which represents the raw materials being released from the dispensary in current production, the entity then move through a decision node where it can be routed n-ways by condition, these conditions include if the queue at the drying ovens exceed 1 then the entity will dispose and wont classify as having being dispensed. If the queues at the drying ovens are less than 1 the entity will flow through the assign node which changes the entity name into a batch, this point is representative of when the dispensed raw material is ready for processing.

The batch entity then is processed by the dry granulation process node for the allocated period of time then by the wet granulation process node for a time. After the dry and wet granulation the batch is put in either one of three ovens, this is done by decide nodes that check whether there is an entity work in progress, if not, the batch entity is routed to the relevant idle resource and processing in the drying node begins. After drying in the ovens for the allocated amount of time the batch is then processed by the crushing node where the material is crushed for a given amount of time.

After crushing the active ingredient is released and added to the batch at the final mixing stage, this forms part of the final mixing stage and does not need to be individually modelled. The product is then mixed for the allotted time and is sent to the compression room where the machines are calibrated and deemed ready to compress, the compression machine then compresses the raw material into tablets, the compressed tablets are then measured for weight and yield, once the batch has passed, the compressed tablets are ready for coating, the coating ingredients are then mixed and added to the machine, the batch of tablets is then added to the coating machine and the coating process begins.

After coating another yield measurement is done and the batch is then signed off for packaging, packaging is not modelled in the simulation as it does not form part of the constrained resources within the production process. The batch entity is then disposed by the dispose node.

7.2.3.5 Step 5 Formulate the problem and plan the study

The problem is that the current production process cannot produce enough tablets to keep up with the demand.

The model study comprises of evaluating the limits of the production process and analysing the output. The limits are achieved when the production process is saturated and queues are increasing beyond resource capability, this will also show the bottlenecks within the system and possible problem areas in the production process

7.2.3.6 Step 6 Validate

The pilot model will be validated against the formulated problem and planned study as well as the batch manufacturing records as stated in section 7.2.3.1.1

Table 20- Batch times

Time

VA Time	Average	Half Width	Minimum Value	Maximum Value
Batch	36.1007	(Insufficient)	34.2297	39.2592

NVA Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Wait Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.02753756	(Insufficient)	0.00	0.4520

Transfer Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Other Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Total Time	Average	Half Width	Minimum Value	Maximum Value
Batch	36.1282	(Insufficient)	34.2297	39.2592

At maximum capacity and close to zero waiting time the model can process a batch on average every 36.13 hours for 100 batches, when looking at the batch manufacturing records it can be seen that the average time for processing is on average 35.5 hours.

A fully processed batch represents 300 000 complete tablets so if 300 000 tablets are produced on average every 10 hours excluding the first batch which is only available 36 hours after the process starts, therefore for a full year of production (8760 hours) the process can produce 874 batches if no stoppages occur this equates to 262.2 million tablets in a full year's production run.

7.2.3.7 Step 7 Design Experiments

- Design Experiment 1: Identify bottleneck at saturation point

Determine the bottlenecks within the process by creating an entity faster than the system can process, identify where queues are out of control and where resource utilization is highest.

- Design Experiment 2: Balance batch dispensing rate with minimal wait time and queue length at bottle neck

To achieve a balance between the dispensing rate and minimal queue lengths it is required to evaluate the bottleneck identified in design experiment 1, this bottleneck's process time represents the fastest time at which the production system can produce the final product.

7.2.3.8 Step 8 Make Production Runs

By making production runs, data will collected on the models performance will be analysed and validated according to Pedgen (1995:147) questions for validating a model, which are;

Does the model adequately represent the real world system (conceptual validity)?

Are the model and the real system behavioural systems similar (operationally validity)?

Does the end user have confidence in the model (believability)?

7.2.3.9 Step 9 Analyse the Output

- Output of Design Experiment 1

At a creation of 5 hours per batch entity the following results were obtained

Table 21 - Design Exp. 1 process and wait times

Time

VA Time	Average	Half Width	Minimum Value	Maximum Value
Batch	36.0532	(Insufficient)	34.1972	38.2006

NVA Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Wait Time	Average	Half Width	Minimum Value	Maximum Value
Batch	97.7763	(Insufficient)	0.4713	194.58

Transfer Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Other Time	Average	Half Width	Minimum Value	Maximum Value
Batch	0.00	(Insufficient)	0.00	0.00

Total Time	Average	Half Width	Minimum Value	Maximum Value
Batch	133.83	(Insufficient)	34.8526	229.91

Table 22 - Design Exp. 1 resource utilization

Resource

Usage

Instantaneous Utilization	Average	Half Width	Minimum Value	Maximum Value
Alexander no.2	0.6407	(Insufficient)	0.00	1.0000
Bin Blender	0.4577	(Insufficient)	0.00	1.0000
Compression Machine	0.9608	(Insufficient)	0.00	1.0000
Diosna p600	0.03452857	(Insufficient)	0.00	1.0000
Drying Oven 1	0.5144	(Insufficient)	0.00	1.0000
Drying Oven 2	0.5227	(Insufficient)	0.00	1.0000
Drying Oven 3	0.5285	(Insufficient)	0.00	1.0000
Lightnin Mixer	0.2125	(Insufficient)	0.00	1.0000
PAC coater	0.8240	(Insufficient)	0.00	1.0000
Scale	0.1371	0.013544788	0.00	1.0000

Table 23 – Design Exp. 1 waiting time at process

Wait Time Per Entity	Average	Half Width	Minimum Value	Maximum Value
Coating	0.06648549	(Insufficient)	0.00	1.5303
Compression	97.3250	(Insufficient)	0.00	194.58
Crushing	0.3426	(Insufficient)	0.00	2.5966
Dry Granulation	0.00	(Insufficient)	0.00	0.00
Drying 1	0.00	(Insufficient)	0.00	0.00
Drying 2	0.00	(Insufficient)	0.00	0.00
Drying 3	0.00	(Insufficient)	0.00	0.00
Final Mix	0.00	(Insufficient)	0.00	0.00
Mix Coating Ingredients	0.00	(Insufficient)	0.00	0.00
Wet Granulation	0.00	(Insufficient)	0.00	0.00
Yield Measurement 1	0.02265130	(Insufficient)	0.00	0.5397
Yield Measurement 2	0.01961019	(Insufficient)	0.00	0.4713

The simulation model show that when the dispensary released a batch for processing every 5 hours the queue at the compression machine starts running out of control, therefore releasing the raw material at a rate of 5 hours per batch is unfeasible as waiting times and queue lengths must be kept to a minimum as the ingredients are sensitive.

- Output of Design Experiment 2

The bottleneck as identified in design experiment 1 is the compression process. The compression process is able to process a batch on average every 7 hours as shown in table 24

Table 24 – Design Exp. 2 Process times

Process

Time per Entity

VA Time Per Entity	Average	Half Width	Minimum Value	Maximum Value
Coating	5.9406	0.016822471	5.5211	6.6155
Compression	7.0350	0.034699075	6.5146	7.9068
Crushing	4.6668	0.017748888	4.1820	5.1443
Dry Granulation	0.1666	0.000420389	0.1571	0.1758
Drying 1	11.3553	(Insufficient)	10.1013	12.8079
Drying 3	11.3472	(Insufficient)	10.0969	12.7972
Final Mix	3.3232	0.012943819	2.8111	3.8115
Mix Coating Ingredients	1.5904	0.042484308	0.7895	2.9223
Set up for Compression	1.0082	0.014098058	0.5455	1.4655
Wet Granulation	0.08320043	0.000268726	0.07397357	0.0939
Yield Measurement 1	0.4518	0.007255412	0.3387	0.6607
Yield Measurement 2	0.5433	0.004253957	0.4688	0.6554

Therefore in order to achieve balance between the dispensing rate and minimal queue length and wait time, the rate of dispensing should equal to the rate at which the compression can process, this is on average 7.035 hours as shown in table 24.

A dispensation rate of 1 batch every 7 hours will achieve a total of 1247 batches each year which equates to 374.1 million tablets.

7.2.4 Production Simulation Conclusion

After investigation and analysis it was determined that the current production process is capable of producing a batch every 8 hours, (refer to Gantt chart in appendix B), based on the simulation model. The simulation model highlighted the constrained resources as well as the process performance that can be achieved based on the resource process times. Answering the objectives of the simulation model, it is clear that the current production process cannot meet the demand. The throughput is affected when the resources are under-utilized, when the dispensing rate is balanced with the bottleneck process times there is a marked increase in production throughput. Based on the demand there are not enough machines and resources available to produce enough medication to meet demand, this is however a costly investment.

The projected increase in demand will see the current production process vastly out matched and serious consideration should be paid to the improvement and expansion of the TB treatment production plant.

8. Recommendations

It is recommended that in order for the production plant to run efficiently and effectively, a tightly managed schedule should be in place. This schedule should be made known to all employees involved in the production process. Machine utilization and idle times should be monitored in order to ensure that the production is operating effectively. The use of visuals aids to highlight the process performance and to keep employees aware in the process a certain batch is located, Kanban cards might prove a viable option which would see the process act more like a lean manufacturing process. A feasibility study should be conducted in order to evaluate whether a new facility or an upgraded facility should be undertaken in order to increase Rifafour e-275 TB medication production.

9. References

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Appendix A

		Start		Complete		Process
Batch no	Process	Date	Time	Date	Time	Time
1343	Dispensing raw materials	31-Jul	08:30			
	Dispensing Coating ingredients	31-Jul	14:00	14-Aug	09:55	
	Granulation	11-Aug	00:15	11-Aug	00:25	00:10:00
	Wet granulation	11-Aug	00:25	11-Aug	00:30	00:05:00
	Drying	11-Aug	04:40	11-Aug	21:20	16:40:00
	Crushing	11-Aug	22:45	12-Aug	03:05	04:20:00
	Final Mix	15-Aug	10:45	15-Aug	13:50	03:05:00
	Set up for compression	15-Aug	14:12	15-Aug	15:30	01:18:00
	Compression	15-Aug	15:30	16-Aug	08:50	17:20:00
	Yield Measurement 1	16-Aug	08:00	16-Aug	08:49	00:49:00
	Mix Coating ingredients	18-Aug	03:45	18-Aug	09:00	05:15:00
	Coating	18-Aug	07:50	18-Aug	12:30	04:40:00
	Yield Measurement 2	18-Aug	17:05	18-Aug	20:45	03:40:00

Batch no	Process	Date	Time	Date	Time	Time
1344	Dispensing raw materials	31-Jul	11:00			
	Dispensing Coating ingredients	02-Aug	10:00	18-Aug	17:40	
	Granulation	11-Aug	11:20	11-Aug	11:30	00:10:00
	Wet granulation	11-Aug	11:30	11-Aug	11:35	00:05:00
	Drying	11-Aug	20:30	12-Aug	20:30	00:00:00
	Crushing	12-Aug	20:50	13-Aug	01:30	04:40:00
	Final Mix	15-Aug	17:00	15-Aug	20:20	03:20:00
	Set up for compression	16-Aug	08:15	16-Aug	10:00	01:45:00
	Compression	16-Aug	10:00	16-Aug	17:04	07:04:00
	Yield Measurement 1	16-Aug	17:17	16-Aug	17:40	00:23:00
	Mix Coating ingredients	18-Aug	14:30	18-Aug	17:45	03:15:00
	Coating	18-Aug	17:05	18-Aug	22:45	05:40:00
	Yield Measurement 2	19-Aug	09:30	19-Aug	10:50	01:20:00

Batch no	Process	Date	Time	Date	Time	Time
1345	Dispensing raw materials	04-Aug	00:15			
	Dispensing Coating ingredients	04-Aug	08:15	19-Aug	19:00	
	Granulation	11-Aug	18:15	11-Aug	18:25	00:10:00
	Wet granulation	11-Aug	18:25	11-Aug	18:30	00:05:00
	Drying	11-Aug	23:00	12-Aug	11:00	12:00:00
	Crushing	12-Aug	15:00	12-Aug	19:40	04:40:00
	Final Mix	16-Aug	10:15	16-Aug	14:55	04:40:00
	Set up for compression	17-Aug	02:50	17-Aug	03:45	00:55:00
	Compression	17-Aug	03:45	17-Aug	09:40	05:55:00
	Yield Measurement 1	17-Aug	09:55	17-Aug	10:20	00:25:00
	Mix Coating ingredients	18-Aug	22:15	19-Aug	07:00	08:45:00
	Coating	19-Aug	07:45	19-Aug	13:20	05:35:00
	Yield Measurement 2	20-Aug	09:50	21-Aug	08:50	23:00:00
Batch no	Process	Date	Time	Date	Time	Time
1346	Dispensing raw materials	04-Aug	00:15			
	Dispensing Coating ingredients	04-Aug	08:15	16-Aug	22:40	
	Granulation	12-Aug	04:15	12-Aug	04:25	00:10:00
	Wet granulation	12-Aug	04:25	12-Aug	04:30	00:05:00
	Drying	12-Aug	11:00	13-Aug	00:00	13:00:00
	Crushing	13-Aug	02:00	13-Aug	05:20	03:20:00
	Final Mix	17-Aug	01:50	17-Aug	04:20	02:30:00
	Set up for compression	17-Aug	15:20	17-Aug	16:00	00:40:00
	Compression	17-Aug	16:00	17-Aug	22:36	06:36:00
	Yield Measurement 1	17-Aug	22:50	17-Aug	23:25	00:35:00
	Mix Coating ingredients	19-Aug	13:30	19-Aug	18:30	05:00:00
	Coating	19-Aug	17:50	20-Aug	00:30	06:40:00
	Yield Measurement 2	20-Aug	08:30	20-Aug	10:00	01:30:00
Batch no	Process	Date	Time	Date	Time	Time
1347	Dispencing raw materials	04-Aug	11:30			
	Dispencing Coating ingredients	05-Aug	05:30	16-Aug	22:40	
	Granulation	12-Aug	09:30	12-Aug	09:30	00:00:00
	Wet granulation	12-Aug	09:30	12-Aug	09:30	00:00:00
	Drying	12-Aug	21:40	13-Aug	08:20	10:40:00
	Crushing	13-Aug	13:30	13-Aug	17:50	04:20:00
	Final Mix	17-Aug	10:50	17-Aug	15:06	04:16:00
	Set up for compression	18-Aug	00:15	18-Aug	00:48	00:33:00
	Compression	18-Aug	00:48	18-Aug	05:20	04:32:00
	Yield Measurement 1	18-Aug	07:40	18-Aug	07:55	00:15:00
	Mix Coating ingredients	19-Aug	23:02	20-Aug	05:00	05:58:00
	Coating	20-Aug	04:30	20-Aug	09:50	05:20:00
	Yield Measurement 2	20-Aug	16:45	20-Aug	22:15	05:30:00
Batch no	Process	Date	Time	Date	Time	Time
1348	Dispensing raw materials	04-Aug	11:30			
	Dispensing Coating ingredients	05-Aug	05:30	16-Aug	22:40	
	Granulation	13-Aug	10:30	13-Aug	10:40	00:10:00

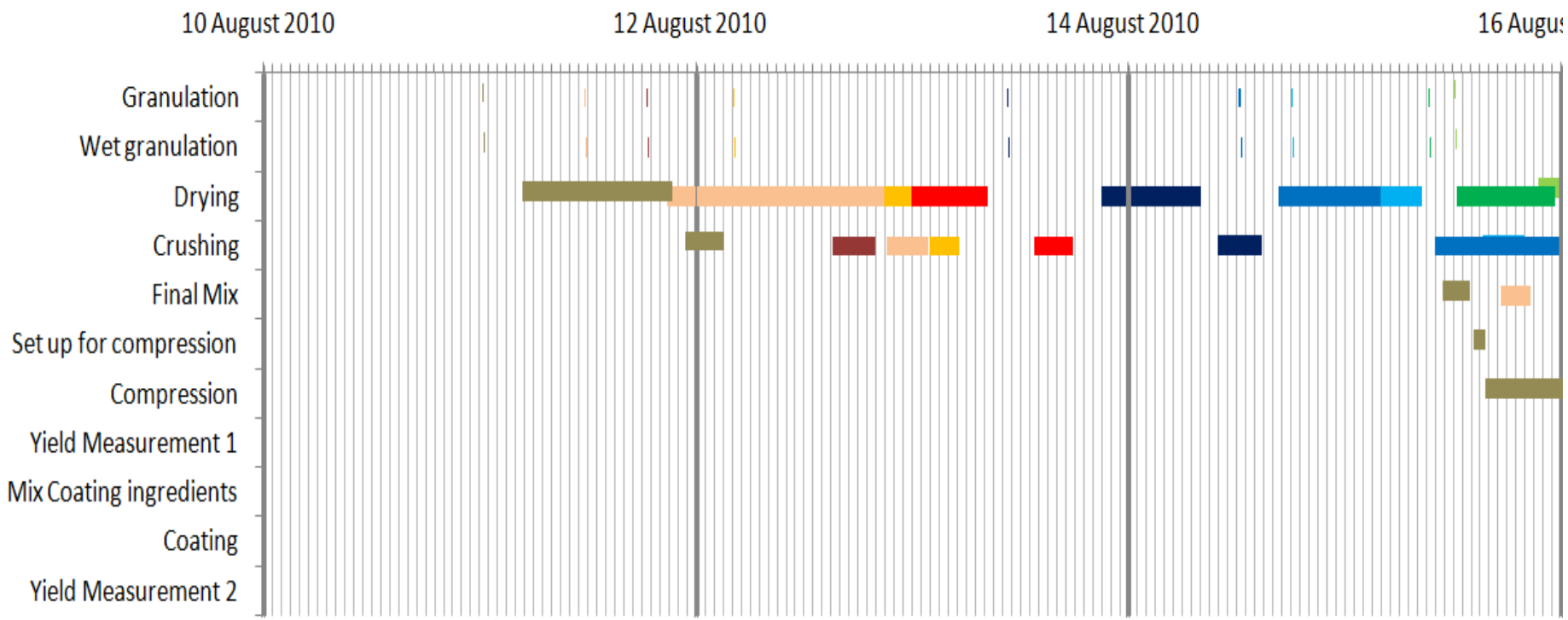
	Wet granulation	13-Aug	10:40	13-Aug	10:45	00:05:00
	Drying	13-Aug	21:05	14-Aug	08:05	11:00:00
	Crushing	14-Aug	09:55	14-Aug	14:50	04:55:00
	Final Mix	17-Aug	17:50	17-Aug	21:30	03:40:00
	Set up for compression	18-Aug	09:55	18-Aug	10:19	00:24:00
	Compression	18-Aug	10:19	18-Aug	16:12	05:53:00
	Yield Measurement 1	18-Aug	16:43	18-Aug	17:10	00:27:00
	Mix Coating ingredients	20-Aug	06:45	20-Aug	14:20	07:35:00
	Coating	20-Aug	14:40	20-Aug	20:40	06:00:00
	Yield Measurement 2	21-Aug	08:50	22-Aug	18:45	09:55:00
Batch no	Process	Date	Time	Date	Time	Time
1349	Dispensing raw materials	06-Aug	03:55			
	Dispensing Coating ingredients	06-Aug	08:15	16-Aug	22:40	
	Granulation	14-Aug	12:10	14-Aug	12:20	00:10:00
	Wet granulation	14-Aug	12:20	14-Aug	12:25	00:05:00
	Drying	14-Aug	16:35	15-Aug	03:55	11:20:00
	Crushing	15-Aug	09:55	17-Aug	21:30	11:35:00
	Final Mix	17-Aug	22:20	18-Aug	10:35	12:15:00
	Set up for compression	18-Aug	18:00	18-Aug	18:27	00:27:00
	Compression	18-Aug	18:27	19-Aug	00:45	06:18:00
	Yield Measurement 1	19-Aug	00:55	19-Aug	01:20	00:25:00
	Mix Coating ingredients	21-Aug	17:30	21-Aug	19:30	02:00:00
	Coating	21-Aug	17:55	21-Aug	23:40	05:45:00
	Yield Measurement 2	22-Aug	13:00	22-Aug	20:50	07:50:00
Batch no	Process	Date	Time	Date	Time	Time
1351	Dispensing raw materials	06-Aug	03:55			
	Dispensing Coating ingredients	06-Aug	08:15	16-Aug	22:40	
	Granulation	14-Aug	18:00			00:10:00
	Wet granulation	14-Aug	18:10	14-Aug	18:15	00:05:00
	Drying	14-Aug	21:30	15-Aug	08:30	11:00:00
	Crushing	15-Aug	15:10	15-Aug	19:45	04:35:00
	Final Mix	18-Aug	18:15	18-Aug	22:10	03:55:00
	Set up for compression	19-Aug	01:30	19-Aug	02:43	01:13:00
	Compression	19-Aug	02:43	19-Aug	07:10	04:27:00
	Yield Measurement 1	19-Aug	07:12	19-Aug	07:35	00:23:00
	Mix Coating ingredients	21-Aug	20:35	21-Aug	21:30	00:55:00
	Coating	22-Aug	12:05	22-Aug	15:25	03:20:00
	Yield Measurement 2	22-Aug	20:25	23-Aug	08:50	12:25:00
Batch no	Process	Date	Time	Date	Time	Time
1351	Dispensing raw materials	06-Aug	17:00			
	Dispensing Coating ingredients	07-Aug	12:55	22-Aug	18:25	
	Granulation	15-Aug	09:20			00:10:00
	Wet granulation	15-Aug	09:30			00:05:00
	Drying	15-Aug	12:30	15-Aug	23:30	11:00:00
	Crushing	16-Aug	10:10	16-Aug	13:50	03:40:00
	Final Mix	18-Aug	22:50	19-Aug	06:50	08:00:00

	Set up for compression	19-Aug	10:20	19-Aug	10:35	00:15:00
	Compression	19-Aug	10:35	19-Aug	17:36	07:01:00
	Yield Measurement 1	19-Aug	17:46	19-Aug	18:07	00:21:00
	Mix Coating ingredients	22-Aug	14:10	22-Aug	18:25	04:15:00
	Coating	22-Aug	19:00	22-Aug	23:50	04:50:00
	Yield Measurement 2	23-Aug	14:00	23-Aug	15:25	01:25:00

Batch no 1352	Process	Date	Time	Date	Time	Time
	Dispensing raw materials	06-Aug	17:00			
	Dispensing Coating ingredients	07-Aug	12:55	24-Aug	22:30	
	Granulation	15-Aug	12:05			00:10:00
	Wet granulation	15-Aug				00:05:00
	Drying	15-Aug	21:30	16-Aug	08:30	11:00:00
	Crushing	16-Aug	18:00	16-Aug	23:15	05:15:00
	Final Mix	20-Aug	01:10	20-Aug	04:55	03:45:00
	Set up for compression	20-Aug	05:40	20-Aug	06:00	00:20:00
	Compression	20-Aug	06:00	20-Aug	13:00	07:00:00
	Yield Measurement 1	20-Aug	13:15	20-Aug	13:40	00:25:00
	Mix Coating ingredients	23-Aug	13:50	23-Aug	16:55	03:05:00
	Coating	23-Aug	16:00	23-Aug	22:20	06:20:00
	Yield Measurement 2	24-Aug	12:40	24-Aug	14:30	01:50:00

Batch no	Process	Date	Time	Date	Time	Time
1353	Dispensing raw materials	10-08-2010		10-08-2010	14:40	
	Dispensing Coating ingredients	23-08-2010		23-08-2010	19:55	
	Granulation	16 August 2010	12:20	16 August 2010	12:30	00:10:00
	Wet granulation	16 August 2010	12:40	16 August 2010	12:45	00:05:00
	Drying	16 August 2010	17:40	17 August 2010	04:40	11:00:00
	Crushing	17 August 2010	07:50	17 August 2010	13:55	05:05:00
	Final Mix	20 August 2010	14:45	20 August 2010	17:47	03:02:00
	Set up for compression	20 August 2010	19:40	20 August 2010	20:00	00:20:00
	Compression	20 August 2010	21:38	21 August 2010	12:25	04:50:00
	Yield Measurement 1	21 August 2010	13:10	21 August 2010	14:55	01:45:00
	Mix Coating ingredients	23 August 2010	20:20	23 August 2010	21:05	00:45:00
	Coating	24 August 2010	10:20	24 August 2010	15:15	03:55:00
	Yield Measurement 2	24 August 2010	21:50	24 August 2010	23:00	01:10:00

Appendix B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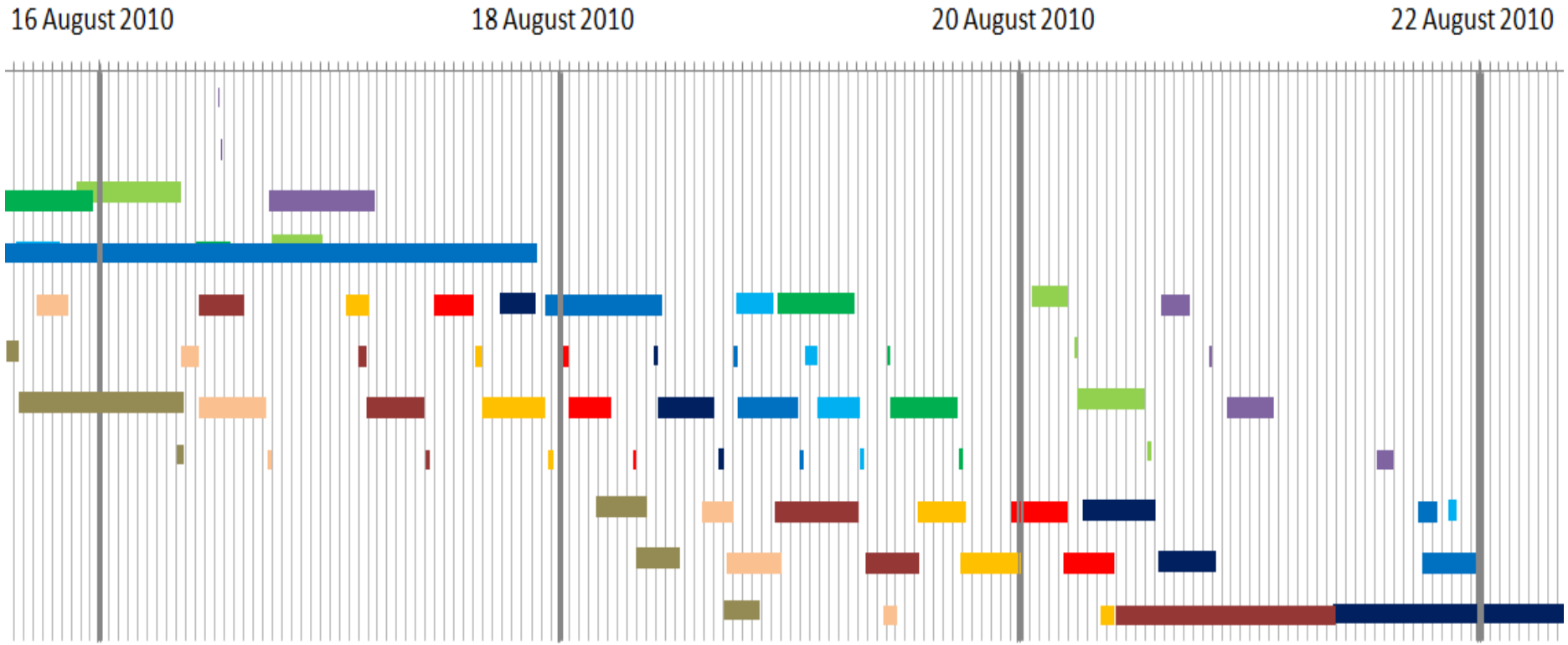
12 August 2010
14 August 2010
16 Augus
Granulation
Wet granulation
Drying
Crushing
Final Mix
Set up for compression
Compression
Yield Measurement 1
Mix Coating ingredients
Coating
Yield Measurement 2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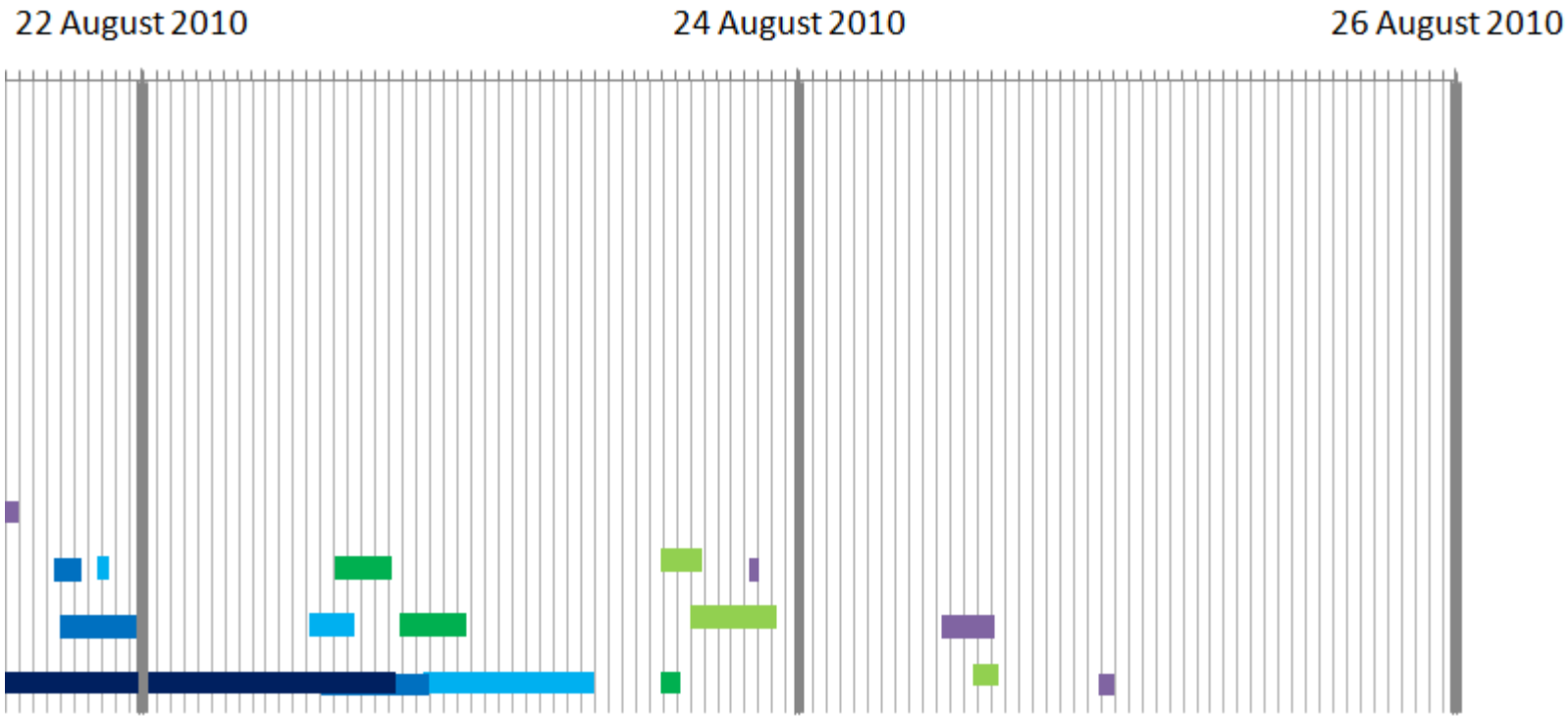
20 August 2010
22 August 2010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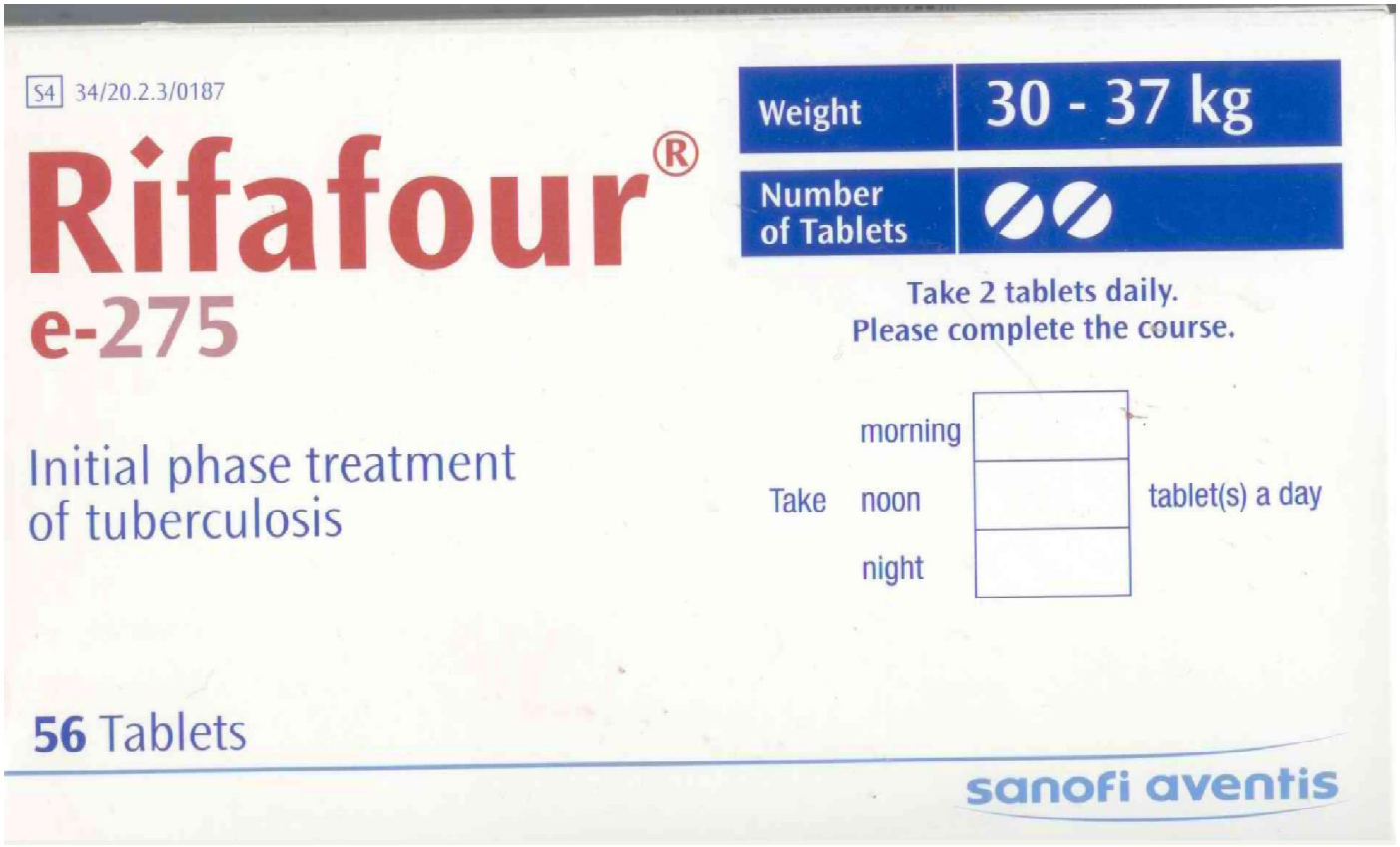
24 August 2010
26 August 2010


S4 34/20.2.3/0187
Rifafour®
e-275
Initial phase treatment
of tuberculosis
56 Tablets
Weight
30 - 37 kg
Number
of Tablets
Take 2 tablets daily.
Please complete the course.
morning
Take noon
night
tablet(s) a day
sanofi aventis