A review of process deviations caused by Human Error in Rottapharm Ltd. from 2006 to 2008

by

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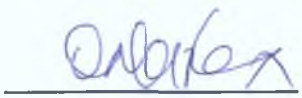
This project is submitted as part of the requirements for the award of the degree of MSc Industrial Pharmaceutical Science.

Declaration

All the work contained herein is my own work absolutely except where otherwise indicated and referenced



Orla Fox

Abstract

The objective of this project is to examine Process Deviation Reports (PDRs) generated from 2006 to 2008 for Sachet Products where "Human Error" has been identified as the primary root cause. Sachet Products were chosen for this review as they represent the largest volume output, and the production process involves the largest number of employees compared to other processes in Rottapharm Ltd. e.g. capsule or tablet production processes. For that reason, it was considered that Human Error PDRs generated during Sachet production represents the "worst-case-scenario" for Human Error PDRs reported at Rottapharm Ltd. From this review, it is intended that trends in Sachet Human Error PDRs will be identified and the effectiveness of corrective actions implemented will be assessed.

Sachet PDRs reported in 2006, 2007 and 2008 were reviewed. The project reports encouraging trends, with the number of PDRs per Sachet output seen to be decreasing from 2006 to 2008.

Retraining and document update (e.g. standard operating procedures, checklists, training manuals etc.) were the primary corrective actions implemented in the period under review. While retraining sessions appear to be effective in the short-term, it is recommended that further medium- and long-term solutions must be found to address Human Error PDRs, e.g. control and monitoring of processes utilising Manufacturing Execution Systems and Process Analytical Technology.

Additional recommendations from this project include increased communication with different departments to highlight Human Error trends to improve awareness and vigilance to these issues. In addition, the approaches of other Irish Healthcare companies in managing Human Error PDRs were reviewed. This concluded that the approach in Rottapharm Ltd. is comparable to that of other companies in the Irish Healthcare Industry.

Acknowledgements

The work contained in this thesis would not be possible without the help and support of many people. Firstly, I would like to thank my supervisor Mary Butler (Institute of Technology, Sligo) for her direction and guidance. I would also like to thank Rottapharm Ltd. for permitting the use and publication of information on deviations reported, processes and quality systems in place

Finally, I would like to dedicate this thesis to my friends, family and Dave, for their support and encouragement which was invaluable throughout.

Abbreviations

API	Active Pharmaceutical Ingredient
APQR	Annual Product Quality Review
CGS	Crystalline Glucosamine Sulphate
GMP	Good Manufacturing Practice
HR	Human Resources
HRT	Hormone Replacement Therapy
IBC	Intermediate Bulk Container
ICH	International Conference on Harmonization
IMB	Irish Medicines Board
IMP	Investigational Medicinal Product
MES	Manufacturing Execution System
PAT	Process Analytical Technology
PDR	Process Deviation Report
PEG	Polyethylene Glycol
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
SOP	Standard Operating Procedure
US FDA	United States Food and Drug Administration

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1.0 Introduction

1.1 Introduction to Rottapharm Ltd.

Rottapharm Ltd. is part of the Rotta Research group, which has its headquarters in Monza, Italy. The parent company was established in 1960 and the company is privately owned. The company's product range is primarily in the therapeutic categories of rheumatology, gastroenterology, osteoporosis and HRT, and is marketed in 62 countries. The main markets are Europe, South America and the Far East. The group has 6 other manufacturing plants in Europe and employs approximately 2000 people in total. The Irish operation commenced in 1998 and the purpose built facility in Mulhuddart, Dublin 15, was opened in June 1999. Rottapharm Ltd. currently employs approximately 150 people.

At the Rottapharm Ltd. facility, finished product in the form of capsules and sachets are produced primarily for the treatment of osteoarthritis. The Active Pharmaceutical Ingredient (API) for these products, Crystalline Glucosamine Sulphate, is also produced at the Dublin facility. The other main product manufactured at the Dublin site is an anti-inflammatory product in the form of tablets, containing the active ingredient Bromelain. Rottapharm Ltd. is also responsible for batch release of a Nitroglycerine transdermal patch called Epinitril/Dermatrans and two medical devices called "GO-ON®" and "GO-ON® Mini". The Nitroglycerine transdermal patch is manufactured by a subcontractor based in Germany. The medical device products are pre-filled syringes containing a Sodium Hyaluronate solution, and are manufactured by a subcontractor based in Austria.

In 2007, the acquisition of the German Madaus Pharma, who specialized in the production of natural pharmaceutics, by the Rottapharm Group strengthened a route already undertaken by many of its brands: from natural origin to active principle. The Rottapharm Group was renamed as Rottapharm|Madaus and change began at Rottapharm Ltd. when the Dublin

facility was identified as a potential back-up to the Madaus Barcelona facility. To enable this, a facility extension was initiated in August 2008 to increase capability at the Dublin site. In 2008, Rottapharm Ltd. commenced introduction and validation of two new products, Plantaben Sachets and Tromalyt Capsules. The introduction of other sachet products utilising the Plantago Ovata Active Pharmaceutical Ingredient (the API in Plantaben Sachets) include Legalon, Colofibre and Spagulax, which are planned for introduction in 2009.

The following pharmaceutical activities at Rottapharm Ltd. are licensed by the IMB (Licence number M868):

- Non Sterile Operations – Solid Dosage Forms:
    - Single Dose Powders
    - Capsules
    - Tablets
- Manufacturing Operations:
    - Manufacture
    - Filling
    - Packaging
    - Storage
    - Testing
    - Distribution
- Other Operations:
    - Batch Release of Transdermal Patches

In addition, the IMB provides GMP certificates stating that Rottapharm Ltd. is a manufacturer lawfully engaged in the manufacture of the active pharmaceutical ingredient Crystalline Glucosamine Sulphate.

Investigational Medicinal Products are also manufactured at the facility (Licence number IMP-017):

- Operations:
    - Manufacture
    - Filling
    - Packaging
    - Storage
    - Testing
    - Distribution

The Quality Policy of Rottapharm Ltd. (as stated in Rottapharm Ltd. Quality Manual, Section 05, Appendix 1) is to produce Pharmaceutical and Medical Device products according to relevant regulations including current Good Manufacturing Practices, the GMP Directive 2003/94/EC and the Council Directive 93/42/EEC concerning medical devices. To this end, Rottapharm Ltd. has established quality systems and procedures, which ensure that the functions, responsibilities and all essential quality criteria associated with the manufacture, storage, packing, testing and delivery of all products are defined. These systems and procedures are designed to ensure compliance with the requirements of regulatory agencies and to meet the needs of our customers and product end-users.

The Quality Assurance Department at Rottapharm Ltd. is responsible for implementation and monitoring of the QA system, which includes Management of the Process Deviation Report (PDR) system.

1.2 Introduction to the Project

The Rules Governing Medicinal Products in the European Union, Volume 4 Part 1, Chapter 1, "Quality Management" requires *that "any significant deviations [from instructions for manufacture; QC sampling, inspection, testing, monitoring of environmental conditions and qualitative/quantitative QC specifications listed in Marketing Authorisation] are fully recorded and investigated".*

Standard Operating Procedure (SOP) QA-SYS-004, "The Process Deviation Reporting System" details the procedure at Rottapharm Ltd. for recording and assessing the impact of deviations from GMP related processes / procedures, for implementing immediate corrective actions, and for implementing preventative actions to prevent recurrence of the deviation. The scope of this SOP is to provide all information relevant to the Process Deviation Report (PDR) system at Rottapharm Ltd. for pharmaceutical products, Active Pharmaceutical Ingredients (API's) and Medical Devices.

For the purposes of this project, Process Deviation Reports generated over the past 3 years will be examined for Sachet Products where "Human Error" has been identified as the primary root cause.

Sachet Products have been chosen for this review as they represent the largest output from Rottapharm Ltd. and the process involves significant staff commitment, thus it is considered that Human Error PDRs generated during Sachet production represents the "worst-case-scenario" for Human Error PDRs reported at Rottapharm Ltd. From this review, it is intended that trends in deviations will be assessed and the effectiveness of corrective actions implemented to reduce frequency of human error deviations can be assessed.

While a product quality review is carried out annually at Rottapharm Ltd. for each product, a 3-year "bigger-picture" review such as this will give a broader perspective and a more accurate evaluation of how systems & corrective actions are impacting on deviation trends over a longer period of time. In

addition to corrective and preventative actions already implemented, a review of proposed future changes and improvements will also be carried out in this thesis.

2.0 Methodological Details

2.1 Overview of the PDR System in Rottapharm Ltd.

What is a PDR?

A PDR is a Process Deviation Report. This report is generated when a deviation occurs at Rottapharm Ltd. A deviation or non-conformance is defined as the non-fulfilment of a specified requirement or an unplanned change from a defined process or procedure.

Who is responsible for reporting a PDR?

Any plant personnel who observe a deviation from a process / procedure are responsible for highlighting and reporting the deviation according to SOP QA-SYS-004. All personnel receive training on this SOP as part of their induction and ongoing/refresher training. Typically, an individual observing a deviation will highlight the fact to the Area Team Leader, Supervisor or Manager, who will complete the initial sections of the PDR form, carry out an initial investigation, and report it to the Quality Assurance Department.

Who is involved in the investigation of a PDR?

Once a PDR is received by the Quality Assurance Department, a PDR meeting is held to discuss the deviation, potential root causes and propose corrective and preventative actions. This discussion involves a multi-disciplinary approach with attendees from areas involved or affected by the deviation and typically includes representatives from Production, Engineering, Warehouse, Quality and a Qualified Person.

How are corrective actions are assigned?

There are two types of actions that are assigned to address a deviation and prevent a recurrence of the deviation:

- *Type 1* actions are generally critical to determining acceptability of a batch or product and must be completed before batch release for

shipment. Examples of Type 1 actions include 100% inspection of the affected portion of the batch to assess level of defects; additional Quality Control testing; review of data, risk assessment, retraining, etc.

- *Type 2* actions are assigned before shipment and may be completed after shipment of the batch. These actions are designed to prevent recurrence of the deviation. Examples of Type 2 actions include SOP update, increase in equipment preventative maintenance frequency, retraining etc.

Actions and target dates are agreed and assigned at the PDR meeting. Completion of Type 1 and 2 actions within agreed time-frames are monitored on an ongoing basis as department metrics. All relevant information, Type 1, Type 2 actions, and their associated target completion dates are recorded on the PDR form and signature approved. The PDR system at Rottapharm Ltd. is paper-based, with a Microsoft Access® Database used to assist tracking of completed or outstanding Type 1 or Type 2 actions.

How are PDRs classified?

The severity of all PDRs is assigned by a Qualified Person. A four digit alpha-numeric code is assigned as outlined below.

The first letter in the code represents the area affected by the PDR:

P = Packaging
M = Manufacturing
E = Engineering
Q = Quality
W = Warehouse
L = Logistics
Z = Plant wide
O = Off site

A number from the following list indicates the primary root cause of the PDR:

1 = Equipment Failure
2 = Human Error
3 = Material Quality
4 = Unknown
5 = System Error
6 = Utility Failure
7 = Design Limitation
8 = Training

A letter from the following list indicates the secondary cause:

S = Material Quality
T = Training
U = Utilities
D = Design Limitations
H = Human Error
N = Unknown
E = Equipment Failure

Finally the severity of the PDR is indicated by a letter from the following list:

M = Minor
S = Serious (Major)
C = Critical

Examples of assigned alpha-numeric PDR codes are presented in the appendices.

The severity of the PDR is determined by the following criteria:

Critical: any deviation, which has had, or could potentially have, an impact on product which could harm a patient.

Major: any deviation, which has had, or could potentially have, an impact on product, which could cause a customer complaint.

Recurring Major PDRs may be reclassified as critical at the discretion of the Qualified Person.

Minor: any deviation, which has not had a significant product impact but nevertheless, represents a deviation from an approved process or procedure. Recurring minor PDRs may be reclassified as Major at the discretion of the Qualified Person.

How are PDRs monitored and trends identified?

(A) Management Review

SOP QA-SYS-006, "The Management Review Process", requires that Management Reviews are carried out on a quarterly basis for Pharmaceutical products. Key Performance Indicators are set as company-wide Quality Objectives at the start of a calendar year, for example, 2008 KPI for PDRs are:

- A reduction of 10% in the number of PDRs per million sachets produced.
- Not less than 80% Type 1 Actions completed within agreed timeframe
- Not less than 75% Type 2 Actions completed within agreed timeframe

Performance of the company and individual departments against these targets is reviewed and discussed at the quarterly meetings.

(B) Product Quality Review

"The Rules Governing Medicinal Products in the European Union", Volume 4, Part 1, Chapter 1, "Quality Management" states that a Periodic Quality Review for a finished product should include "a review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken".

Rottapharm Ltd. SOP QA-SYS-010, "The Annual Product Quality Review" (APQR) requires that all aspects relating to the quality of each product manufactured at Rottapharm Ltd. is reviewed and reported on an annual basis. The APQR report includes an examination of PDRs generated and a review of the effectiveness of corrective actions implemented during the year

in question.

How are potential PDRs identified and prevented?

(1) Quality risk management

"The Rules Governing Medicinal Products in the European Union", Volume 4, Part 1, Chapter 1, "Quality Management" and Annex 20 defines Quality Risk Management as a *"systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product"*.

Rottapharm Ltd. SOP QA SYS-061, "Risk Management Policy" is closely based on Annex 20 and defines the policy and procedures for risk management within Rottapharm Ltd. It is often used in conjunction with the implementation of changes, which are managed through the Rottapharm Ltd. Change Control System (SOP QA-SYS-009). During the assessment of a planned change to a process (including manufacturing process, analytical method, facility, product etc.) risk management principles are carefully considered to ensure any proposed change does not adversely impact on the product manufactured, existing products, or activities that are concurrent in GMP facility.

"The Rules Governing Medicinal Products in the European Union", Volume 4, Part 1, Chapter 9, "Self Inspection" requires that *"self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures"*. Rottapharm Ltd. SOP QA-SYS-015, "Internal Quality Auditing Programme" works to this aim, with all GMP areas and pharmaceutical processes audited on a regular basis according to a predefined audit schedule.

The PDR system at Rottapharm Ltd. is paper-based, with a Microsoft Access® Database *"PDR Database"* used to assist tracking of PDR approval, completed or outstanding actions etc. The database is maintained by the Quality Assurance department, who are responsible for inputting all PDR

details along with corrective/preventative actions (i.e. Type 1 and 2 actions). All company personnel have 'read-only' access to the database, which allows staff to track completion of all actions. Department queries have been created in the PDR database, which allows any department to obtain 'live' lists of outstanding actions e.g. the Quality Control query can be used by the Quality Control Manager to extract a list of all QC open actions from the PDR database. The objective of this 'query' function is to facilitate departments in managing on-time closure of their PDR actions.

2.2 Overview of CGS Sachet Manufacturing/Packaging Process

CGS sachet blend sizes are 800 Kg and 2400 Kg. For the 800 Kg sachet blend, the raw materials are weighed and sieved through a vibratory sieve fitted with a 900µm mesh prior to charging into a 1500 litre Intermediate Bulk Container (IBC).

For the 2400 Kg blend, the raw materials are charged into a 3500 litre Hosokawa blender located in Process Room M9. In this case, the Crystalline Glucosamine Sulphate and the Sorbitol ingredients are dispensed from weight controlled bag discharge stations located via a vacuum transfer system to the static blender. Remaining excipients are also transferred into the blender using the vacuum transfer system.

The sachet mix is blended according to a defined speed and time in a Matcon Blender. The IBC containing the sachet blend is then stored until required at which point it is transported to the assigned sachet room for filling.

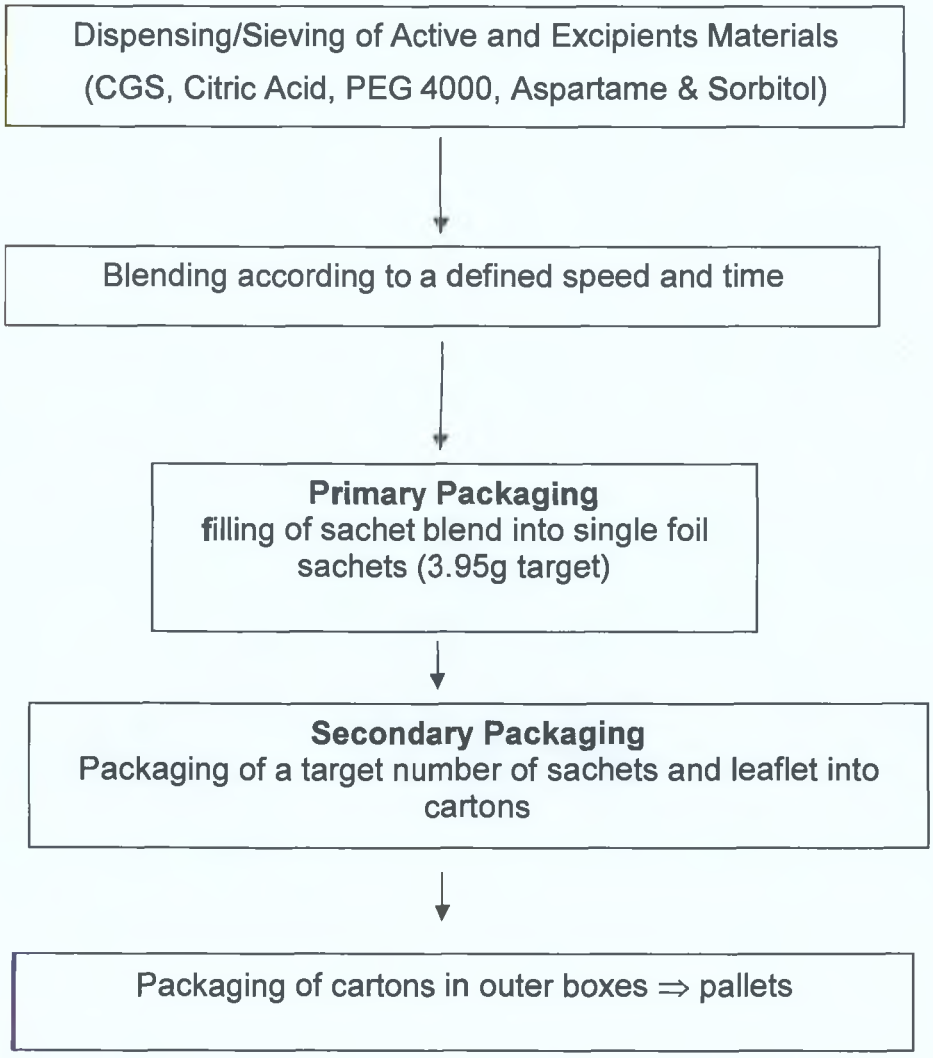
In both cases (i.e. 800Kg or 2400Kg batch size), primary and secondary packaging is identical and carried out on either Sachet Line 1 or 2. Primary packaging involves the automatic filling of blend into sachets using a Marchesini Sachet Filler. Sachets are secondary packaged via the on-line insertion of a target number of sachets and information leaflet into a finished product carton using a BA Cartoner. Cartons are then automatically packed into outer boxes prior to moving to the warehouse, in preparation for shipping.

Sachet Lines 1 and 2 are fitted with the following modules to carry out in-line process checks to assure the quality of the finished product:

- PharmAssist Sachet Checkweigher
- Prisma Carton Checkweigher
- Pharmacode Monitoring System for leaflets and cartons
- Metler-Toledo X-Ray Inspection Units.

The process flow of the CGS Sachet manufacturing and packaging process is outlined below. The process flow for Plantaben Sachets is essentially similar with different materials, blending conditions and target weights applied.

CGS Sachet manufacturing and packaging process:



2.3 Methods used to analyse the data

For this project, data from the Microsoft Access® PDR database for the years under examination were exported into a Microsoft Excel® Spreadsheet where it was manipulated to provide the necessary comparisons with respect to product and primary root cause, i.e. Sachets and Human Error.

This above information, in conjunction with the QA Summary Report and QP Final Report, were utilised to identify the corrective and preventative actions implemented at the time of the PDR investigation. The QA Summary Report is prepared by a member of the Quality Assurance department when all Type 1 actions have been completed and when Type 2 actions have been agreed. This Summary Report includes a complete review of the primary root cause of PDR, what Type 1 (corrective) actions were applied to address the deviation prior to batch release, and what Type 2 actions have been agreed which will prevent recurrence of the PDR. This report is reviewed by the Qualified Person prior to making their batch disposition decision. Once the Type 2 actions are completed, the Qualified Person completes the QP Final Report section of the PDR Form. This report includes an assessment of the Type 2 (preventative) actions applied, and the rationale for their batch disposition decision.

A review of all Sachet Human Error PDRs for 2006 to 2008 was also carried out to identify potential reoccurrence of the same issues and thus assess the effectiveness of the original corrective actions implemented.

3.0 Results

Appendices I, II and III summarise the details, severity and primary and secondary root cause of Sachet PDRs reported in 2006, 2007 and 2008. The data in these appendices was analysed to quantify data by product type, by severity and by primary root cause (Human Error), to evaluate the corrective actions assigned to address the primary root cause. This data is presented in Sections 3.1, 3.2, 3.3 and 3.4.

3.1 2006 PDRs

Table 3.1 and Chart 3.1 demonstrate the breakdown of the total PDRs reported by primary root cause. It is evident that the highest occurrence is for Equipment Failure and Human Error.

Table 3.1

	Primary Root Cause	**%**
Equipment Failure	56	*35*
Human Error	52	*33*
Material Quality	16	*10*
Unknown	25	*16*
System Error	5	*3*
Utility Failure	2	*1*
Design Limitation	2	*1*
Training	1	*1*
Total	*159*	

Chart 3.1

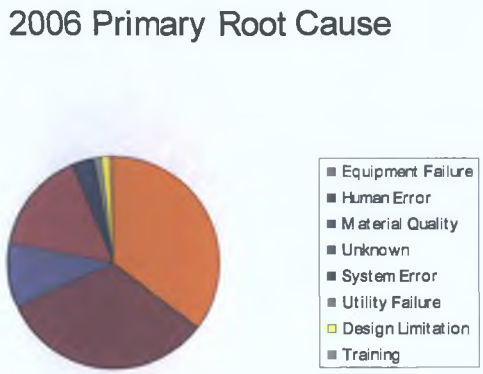


Table 3.2 and Chart 3.2 demonstrate the breakdown of the total 2006 PDRs reported by severity. A significant number of PDRs (75%) were for unsealed or badly cut sachets and were classified as Major due to their recurring nature and the potential for a customer complaint to be reported, had the defect not been detected. The majority of other PDRs were classified as minor in nature.

Table 3.2

Severity	#	%
Minor	79	50
Serious (Major)	76*	48
Critical	4	3

Chart 3.2

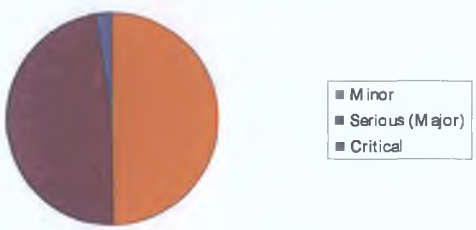


Table 3.3 and 3.4 demonstrate the quantity and severity of 2006 Sachet PDRs caused by Human Error.

Table 3.3

Total no. PDRs	**159**
No. Sachet PDRs	59
No. Sachet PDRs caused by Human Error	15
% of sachet PDRs caused by Human Error	25

Table 3.4

Severity	**# Human errors**	**% Human errors**
Minor	7	14
Major	8	16
Critical	0	0

Table 3.5 demonstrates the types of corrective actions that were applied to 2006 Human Error Sachet PDRs.

Table 3.5

Types of Corrective Actions applied.	**# instances**
Retraining	14
Documentation Update. E.g. training manual, SOP, Batch Records	8
Other? E.g. HR involvement, disciplinary proceedings	1

3.2 2007 PDRs

Table 3.6 and Chart 3.3 demonstrate the breakdown of the total PDRs reported by primary root cause. It is evident that the highest occurrence is for Equipment Failure, Human Error and Unknown.

Table 3.6

	Primary Root Cause	%
Equipment Failure	61	*33*
Human Error	57	*30*
Material Quality	6	*3*
Unknown	49	*26*
System Error	2	*1*
Utility Failure	0	*0*
Design Limitation	10	*5*
Training	2	*1*
Total	*187*	

Chart 3.3

2007 Primary Root Cause

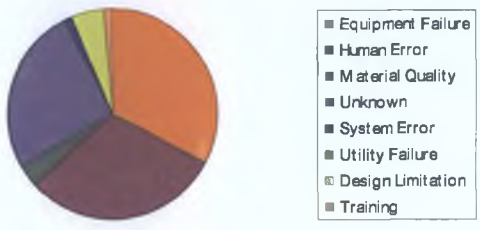


Table 3.7 and Chart 3.4 demonstrate the breakdown of the total 2007 PDRs reported by severity. A significant number of PDRs (85%) were for unsealed or badly cut sachets and were classified as Major due to their recurring nature and the potential for a customer complaint to be reported, had the defect not been detected. The majority of other PDRs were classified as minor in nature.

Table 3.7

Severity	#	%
Minor	67	36
Serious (Major)	120	64
Critical	0	0

Chart 3.4

2007 PDR Severity

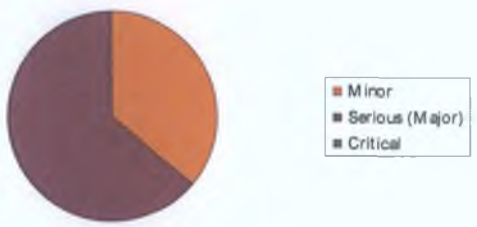


Table 3.8 and 3.9 demonstrate the quantity and severity of 2007 Sachet PDRs caused by Human Error.

Table 3.8

Total no. PDRs	187
No. Sachet PDRs	93
No. Sachet PDRs caused by Human Error	18
% of sachet PDRs caused by Human Error	19

Table 3.9

Severity	# Human errors	% Human errors
Minor	5	10
Major	13	26
Critical	0	0

Table 3.10 demonstrates the types of corrective actions that were applied to 2007 Human Error Sachet PDRs.

Table 3.10

Types of Corrective Actions applied.	# instances
Retraining	16
Documentation Update. E.g. training manual, SOP, Batch Records	6
Other? E.g. HR involvement, disciplinary proceedings	0

3.3 2008 PDRs

Table 3.11 and Chart 3.5 demonstrate the breakdown of the total PDRs reported by primary root cause. It is evident that the highest occurrence is for Equipment Failure, Human Error and Unknown.

Table 3.11

	Primary Root Cause	%
Equipment Failure	74	*45*
Human Error	62	*38*
Material Quality	3	*2*
Unknown	20	*12*
System Error	2	*1*
Utility Failure	0	*0*
Design Limitation	2	*1*
Training	0	*0*
Total	*163*	

Chart 3.5

2008 Primary Root Cause

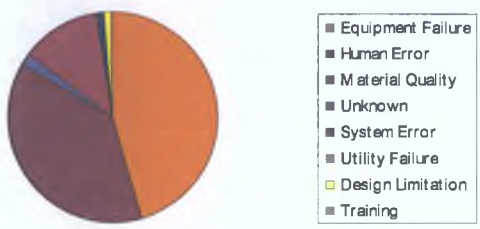


Table 3.12 and Chart 3.6 demonstrate the breakdown of the total 2008 PDRs reported by severity. A significant number of PDRs (61%) were for unsealed or badly cut sachets and were classified as Major due to their recurring nature and the potential for a customer complaint to be reported, had the defect not been detected. The majority of other PDRs were classified as minor in nature.

Table 3.12

Severity	#	%
Minor	89	55
Serious (Major)	74*	45
Critical	0	0

Chart 3.6

2008 PDR Severity

Table 3.13 and 3.14 demonstrate the quantity and severity of 2008 Sachet PDRs caused by Human Error.

Table 3.13

Total no. PDRs	**163**
No. Sachet PDRs	**77**
No. Sachet PDRs caused by Human Error	26
% of sachet PDRs caused by Human Error	*34*

Table 3.14

Severity	# Human errors	% Human errors
Minor	17	65
Major	9	35
Critical	0	0

Table 3.15 demonstrates the types of corrective actions that were applied to 2007 Human Error Sachet PDRs.

Table 3.15

Types of Corrective Actions applied.	# instances
Retraining	23
Documentation Update. E.g. training manual, SOP, Batch Records	6
Other? E.g. HR involvement, disciplinary proceedings	1

3.4 Comparison of 2006, 2007 and 2008 PDR Data

Table 3.16 compares the total number of PDRs per million sachets reported per year.

Table 3.16

Year	Total # PDRs reported	# Million Sachets Produced	Total # PDRs per million sachets	% change on previous year
2006	159	164	0.970	N/A
2007	187	185	1.011	+4%
2008	163	196	0.832	-18%

Table 3.17 compares the total number of Sachet PDRs per million sachets reported per year.

Table 3.17

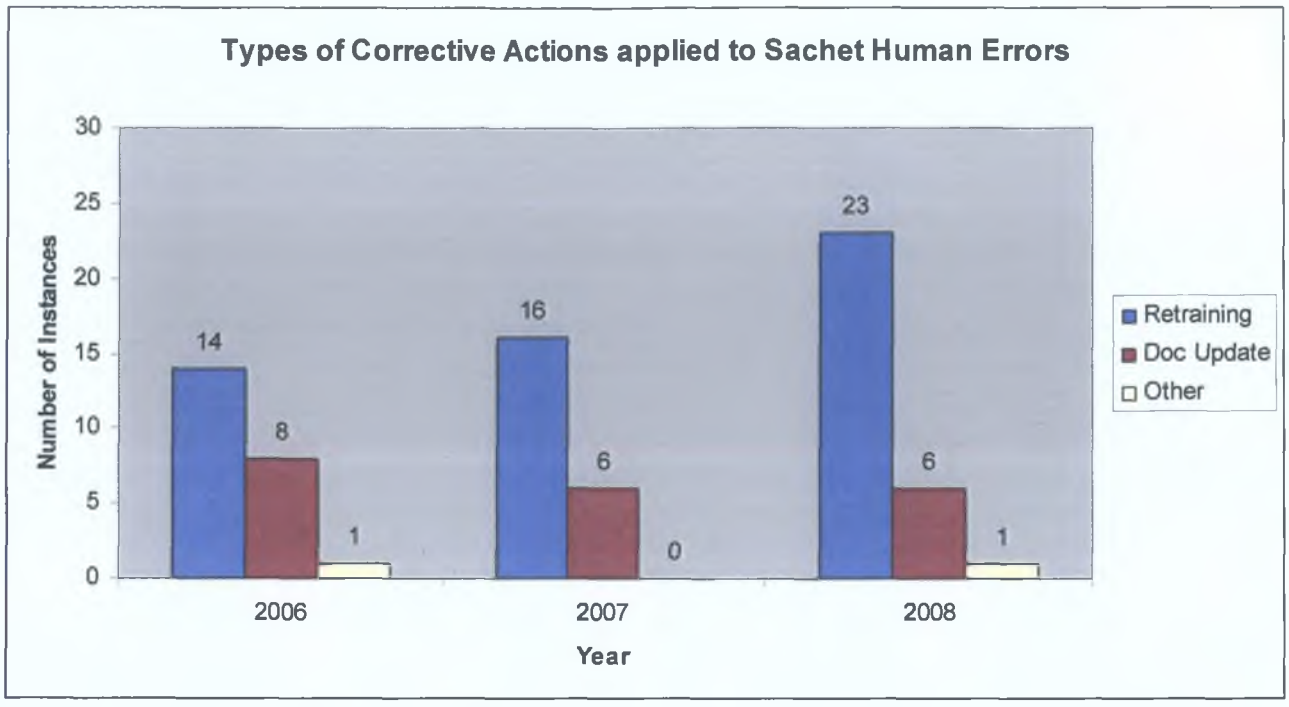
Year	# Sachet PDRs	# Million Sachets Produced	# Sachet PDRs per million sachets	% change on previous year
2006	59	164	0.359	N/A
2007	93	185	0.502	+40%
2008	77	196	0.393	-22%

Table 3.18 and Chart 3.7 compare the types and instances of corrective actions implemented for Sachet Human Error PDRs per year.

Table 3.18

	# instances		
Types of Corrective Actions applied.	2006	2007	2008
Retraining	14	16	23
Documentation Update	8	6	6
Other	1	0	1

Chart 3.7


Types of Corrective Actions applied to Sachet Human Errors
Number of Instances
30
25
20
15
10
5
0
14
8
1
16
6
0
23
6
1
2006
2007
2008
Year
Retraining
Doc Update
Other

4.0 Discussion

4.1 Sachet Human Error PDRs

The largest root cause of PDRs in 2006 was Equipment Failure (35%), followed by Human Error (33%) (Table 3.1). When examining Sachet PDRs specifically, it is observed that 25% (15 out of 59 Sachet PDRs) were caused by Human Error (Table 3.3). These Sachet Human Error PDRs and their respective corrective actions were reviewed in accordance with 2007 and 2008 PDRs to assess the effectiveness of actions implemented to prevent reoccurrence of the issue.

In 2006, three Sachet PDRs were caused by deficiencies in the Engineering Training Manuals. In one instance (PDR-06-004-S), over adjustment of equipment parameters during an engineering intervention caused badly cut sachets to occur. In the second instance (PDR-06-161-S), a screw removed during equipment maintenance was found in a carton of sachets. PDR-06-097-S also reported a screw found in a carton for the same reason. These specific PDRs were addressed by an update to Engineering Training Manuals, which all Technicians were subsequently trained on. These specific issues did not reoccur during the rest of 2006 or throughout 2007, confirming the effectiveness of the action taken. The Engineering Training Manuals required further update in 2007 as result of two PDRs; to include a requirement to advise Production Operators prior to the power-down of equipment in-use, and to include a requirement that while necessary engineering maintenance work is on-going, any and all product produced during that time must be rejected. The updates to the Engineering Training Manuals carried out in 2006 and 2007 are considered to be effective as PDRs have not reoccurred for the same reasons, with two exceptions in 2008: (A) PDR-08-132-S and (B) PDR-08-028-S, which resulted (A) in an incorrect expiry date being applied to cartons caused by Engineering Technicians not advising Production that printer was powered down and (B) a screw removed during maintenance work was found in a carton caused by an Engineer not reconciling screws following

maintenance work. Both of these issues had been included in Engineering Training Manuals in 2006 and 2007, and the specific Technicians were retrained in 2008. No further reports of these types of PDRs arose in the latter part of 2008, but this will require to be further monitored to assure the continued effectiveness of the Engineering Training Manuals and the retraining provided in 2008.

Due to the number of PDRs reported relating to incorrect material check-in in late 2005, a 'Material Check-in Training Module' was introduced to ensure production, warehouse and quality personnel received specific training in this subject. The effectiveness of this training was demonstrated by the fact that no Sachet deviations were reported relating to material check-in during 2006 and 2007 (Appendix I and II). One Sachet PDR was reported in 2008 due to Human Error during material check-in (PDR-08-086-S). The root cause was attributed to staff turnover since initial training on the original 'Material Check-in Training Module', and that all new staff employed since 2006 had not completed the training module. Corrective action to address this was to complete Material Check-in training with all personnel who had not received the original training. In addition, training on Material Check-in is now to be delivered to all new employees in these areas. This had not previously been monitored to ensure new staff completed this training module as part of their standard induction and job/task training, but it has since been initiated by the Training Coordinator. SOP PRO-GEN-025, "Task Training Procedure for Production Personnel at Rottapharm Ltd." details production and warehouse department specific training requirements. The current procedure requires that a controlled 'Task Training Manual' which details the training requirements for a specific "task" is issued to a trainee by the Training Coordinator.

SOP PRO-GEN-025 contains a list of approved Task Training Manuals and was last updated in March 2008, but it does not refer to the 'Material Check-in Training Module'. While the corrective action resulting from PDR-08-086-S will ensure in the short term that the issue does not reoccur, it does not provide for a longer-term prevention and if not proceduralised, there is a risk that the issue could reoccur. It is recommended that SOP PRO-GEN-025 be updated

to include the 'Material Check-in Training Module' to address this.

The highest root cause of PDRs in 2007 was Equipment Failure (33%), followed by Human Error (30%) and Unknown (26%), where the exact root cause was not evident (Table 3.6). When examining Sachet PDRs specifically, it is observed that 19% (18 out of 93 Sachet PDRs) were caused by Human Error in 2007 (Table 3.8).

While the total number of PDRs reported in 2007 (185 PDRs) appears to have increased in direct comparison with 2006 (159 PDRs), this does not take into account of the increase in output volumes (Table 3.16). To normalise the annual figures and compare 'like-with-like', output volumes must be taken into consideration to give a more accurate reflection of the performance per year in terms of PDRs. When comparing the total number of PDRs to Sachet output, a 4% increase in the total number of PDRs per million sachets between 2006 and 2007 is observed (Table 3.16). The minor increase was reversed in 2008, with the number of PDRs per million sachets decreasing by 18% compared to 2007. Overall, the performance in terms of PDRs has improved over the three year period with a decrease from 0.970 PDRs per million sachets in 2006 to 0.832 PDRs per million sachets in 2008 (Table 3.16).

Speed increases and improved efficiencies on the Sachet Lines during 2007 and 2008 contributed to the overall reduction in PDRs per million sachets, the most significant being the completion of a six-sigma project into unsealed and badly cut sachets. Problems with these defects had previously resulted in a significant number of PDRs, with Equipment Error and Unknown the primary root causes assigned. This project commenced in late 2006 and continued throughout 2007. The objective of the 2006/2007 six-sigma project was to identify possible causes and implement actions to reduce occurrences of unsealed and badly cut sachets to improve product quality and improve efficiency of the line by reducing rework and 100% inspections. The main recommendations from the project included (among others) increased frequency of preventative maintenance of the sachet fillers, and improved

cleaning of Intermediate Bulk Containers (IBCs); more specifically improved drying of these containers; as it was found that moisture can cause lumps in blends which can cause problems during filling and contribute to unsealed sachets. The numbers of instances of unsealed/badly cut sachet defects observed during inspections were trended in 2007 to assess and monitor the performance of the process. In the Rottapharm Ltd. 2007 Annual Product Quality Review report for CGS Sachets, results were presented that showed a decrease in the number of instances of these defect types throughout 2007 to below the six-sigma defect level. The number of defects per inspection will continue to be monitored to ensure the process continues to achieve the six-sigma defect level.

Incorrect or missing variable data on cartons was an issue during 2007; with 6 out of 18 Human Error Sachet PDRs being reported for this issue (PDR-07-004-S, PDR-07-041-S, PDR-07-058-S, PDR-07-068-S, PDR-07-071-S, and PDR-07-103-S). Missing variable data was addressed by retraining in two instances and an update to Engineering Training Manual in one to ensure Production Operators are immediately notified of any power-down of equipment during production. Incorrect variable data (e.g. incorrect price or expiry date) was determined to be caused by poor or absent second checks and resulted in retraining for personnel involved. The corrective actions implemented were effective in reducing this type of PDR with only one occurrence reported in 2008 (PDR-08-026-S) whereby an incorrect date of manufacture was recorded on cartons. This was again addressed by retraining and the issue has not reoccurred since. While individual retraining sessions appear to be effective, it is recommended that department-wide and inter-department communication of PDR root causes be introduced on an ongoing basis to increase awareness and vigilance of such issues.

While two other instances of incorrect variable data were reported in 2008, these were treated separately as they had unique root causes unrelated to those previously observed. PDR-08-132-S was discussed previously and was caused by Engineering not advising Production that printer was powered down. PDR-08-126-S was reported as an incorrect batch number was

assigned as XXA on issued batch documentation, where it should have been XXB. The root cause was identified as be Human Error and was attributed to a combination of inexperience and a lack of training, as the specific product presentation was not routine and the 'back-up' Document Controller had not encountered it to this point. The error was highlighted by production in advance and was corrected before any product was packaged, thus there was no product impact. The 'back-up' Document Controller was subsequently trained on this specific product presentation.

In July 2007, two instances of contaminated Sachet Blend were reported with a root cause of Human Error. PDR-07-116-S and PDR-07-123-S reported contamination of Sachet Blend with blue nitrile glove and nylon cable, respectively. Disposable gloves were removed from the area and the API bulk production SOP's were updated to detail use and cleaning of heavy duty gloves. All API bulk operators received training on the new SOP and on general contamination minimisation procedures. This corrective action was effective as this type of PDR has not reoccurred to date.

The largest root cause of PDRs in 2008 was Equipment Failure (45%), followed by Human Error (38%) (Table 3.11). When examining Sachet PDRs specifically, it is observed that 34% (26 out of 77 Sachet PDRs) were caused by Human Error in 2008 (Table 3.13).

There were two significant events that impacted the Sachet Line in 2008.

(A) 2008 saw the introduction of a new product (Plantaben) to the Sachet Lines. Prior to this, the Sachet Lines were dedicated to one product – Crystalline Glucosamine Sulphate. This project involved the introduction of new materials, cleaning procedures, batch files and other general procedures to the Area. Trials were carried out in May, validation of the process took place in August, and the product went into routine production in November. Training and other requirements were managed through the change control system.

(B) November 2008 also saw the introduction of a third (night) shift for the

sachet packaging lines. This meant that equipment was running for 50% longer per working day and a number of newly recruited personnel were introduced into engineering, production, warehouse and quality roles.

The extra workload for equipment was assessed with respect to preventative maintenance and parts replacement to ensure process efficiency and product quality were not compromised. New preventative maintenance and equipment/area cleaning schedules were put in place.

To allow for the fact that night shift staff would not have the same support network as day/evening shift staff do, in terms of numbers of other staff and management on-site, existing experienced employees from engineering, warehouse, production and quality were moved to the night shift. While some of their positions were back-filled by existing employees, some were filled with new recruits. During day/evening shifts there is more staff on-site, which affords the required training and supervision needed for new staff.

2008 PDRs other than those already discussed were reviewed. They were addressed by retraining and/or document updates, e.g. SOP, batch record, etc. and were considered to be isolated issues and not constituting an adverse trend.

4.2 Current procedures for managing Human Error PDRs at Rottapharm Ltd.

4.2.1 Training as a Preventative Action (Initial Training, Refresher Training, and prior to Implementing a Change)

The Rules Governing Medicinal Products in the European Union, Volume 4 Part 1, Chapter 2, "Personnel" requires *that "all personnel should be aware of the principles of Good Manufacturing Practice (GMP) that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs".*

To meet this requirement, initial and refresher GMP training is provided to all employees on an ongoing basis, and is outlined in SOP FAC-GEN-001, "General Training Procedure". New recruits receive GMP training as part of induction. All employees receive refresher GMP training on an annual basis. At Rottapharm Ltd. the refresher GMP training programme includes a section on the PDR system with some 'real' examples that personnel can easily identify with, to remind them to ensure that any departures from approved procedures are reported if observed. While this is a requirement of the quality system, it was noted during research for this project that it is currently not defined where the responsibility lies for managing the refresher GMP training programme, i.e. if it is

- Quality Assurance (who are responsible for delivering the training);
- Human Resources (who have responsibility for administering training system); or
- Individual department managers (who are responsible for ensuring their employees are fully trained)?

As responsibility for the management of the facility refresher GMP

training programme is not currently defined, there is a risk that not all personnel will receive refresher training in compliance with SOP FAC-GEN-001. To address this 'gap' in the system, it is recommended that SOP FAC-GEN-001, "The Training Procedure at Rottapharm Ltd." be updated to incorporate the following:

- Definition of the persons/department responsible for managing the refresher GMP training programme.
- A schedule for routine refresher GMP training that can be tracked and progress monitored at the quarterly Management Reviews.

In addition to initial and refresher training, training delivered following new process/product/equipment introduction or a change to existing process/product/equipment is also carried out. Training requirements are evaluated using the principles of quality risk management during the change control process and managed via change control system, whereby responsible persons and target completion dates are agreed, and documented evidence of completion must be presented to change controller prior to closure of the "action" and approval by a Qualified Person to proceed with the proposed change.

4.2.2 Training as a Corrective Action (Retraining as corrective action following a PDR)

Retraining can be a short-term corrective action and does not always prevent reoccurrence of a PDR. While individual retraining sessions appear to be effective in the short-term, it is recommended that department-wide and inter-department communication of PDR root causes be introduced to increase awareness and vigilance of such issues on a routine basis. Improved awareness and involvement from personnel at all levels/positions is necessary in ensuring employees remain vigilant to prevent potential Human Error PDRs.

Human error as a root cause of deviations cannot completely be eliminated while humans are involved in processes, but they can be controlled and minimised. Planned future changes to limit and control Human involvement with processes should see a reduction in PDRs caused by Human Error.

4.3 Industry Benchmarking

A cross-section of approaches from industry to managing Human Error PDRs was reviewed.

Table 4.1

Company	Business	Number of Employees
Company A	A specialty pharmaceutical development company	<100 employees
Company B	A leading manufacturer of solid oral and parenteral medicines	100 - 500 employees
Company C	A multinational biopharmaceutical company	>1,000 employees
Rottapharm Ltd.	Solid oral dosage manufacturer	~150 employees

Approach of Company A and Company C:

If a PDR or error is reported, a root cause must be identified. A root cause of "Human Error" may result in retraining of the individual(s) or document update e.g. SOP, checklist, batch record, etc.

In addition, in Company C the individual is 'counseled' by the Area Manager, i.e. they are made aware of the exact error, the investigation and the correct way they should have proceeded. Also, the individual is involved in writing up the investigation and conclusion to ensure a full understanding of the issue. Area Managers also carry out communications with the different shifts to emphasis human error trends so that it's not just one particular individual getting the benefit of the counseling but the entire team.

Approach of Company B:

In Company B, "Human Error" is not an optional root cause for a PDR, and retraining is not optional corrective action. Examples of classification of "Human Errors" in Company C include "Application Errors", "Omission Errors", "Learning Gaps", etc. The specific root cause for the PDR must be identified and corrective action should incorporate a change to a process, document or SOP to improve or clarify the process; the process is considered deficient is a person can make an error. Once the process deficiency is addressed, personnel are trained on the new process. The aim of this system is to move away from ineffective retraining or token procedure updates and put 'physical barriers' in place to make it impossible for personnel to make the same mistake twice, i.e. 'mistake proofing'. For example, a PDR is reported due to a mix-up between two similar looking reagents in a press. The corrective action may be to move one of them to a different location, or label with different colour labels to make them physically different.

The approach in Rottapharm Ltd. is similar to that of Companies A and C. With previous recommendations from this project including increased communication with different departments to highlight Human Error trends, awareness and vigilance to these issues will be further improved.

It is also recommended that the process of assigning the root cause of a PDR is reviewed, to ensure that "Human Error" is not being assigned as a 'catch-all' root cause and that the true root cause of a PDR is identified. To support this, external training on Root Cause Investigation has been planned for completion in 2009 for employees involved in investigating PDRs. When reviewing the PDR investigation process with respect to correct root cause identification, the approach of 'mistake proofing' as a corrective action, will be reviewed by Rottapharm Ltd. for potential implementation.

4.4 Planned future changes & improvements

A Manufacturing Execution System (MES) with electronic batch records is planned to be implemented in Rottapharm Ltd. with the following capabilities:

- Current labelling system to be replaced with a barcode scanning system to prevent incorrect material picked by warehouse and/or dispensed by production – the Warehouse module is planned for implementation in June 2009, with the Production module to follow by 2010.
- Paper-less (or much reduced) system with hand-held notebook computers (Electronic Batch Records replacing paper Batch Records)
- Removing or at least reducing Human/Equipment interfaces with process equipment
- Cannot proceed to next stage of processing if there is a step incomplete or incorrectly completed
- Pass/fail options for in-process checks, and cannot proceed if fail
- Secure operator/approver options
- QA batch file review will be 'review by exception' – greatly simplified & reduction in review times for Quality Assurance and Qualified Person.

Development of new technologies such as Process Analytical Technology (PAT) for use in Pharmaceutical industry also opens opportunities for companies to improve the quality of their product and thus reduce errors, batch reject/rework and production down-time to mention a few benefits. These benefits reduce labour costs and improve batch turnaround times, which reduce product costs and in-turn improve company cost effectiveness in an increasingly more competitive market.

Process Analytical Technology is defined by the US FDA as *"a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality".*

The US FDA have identified that the desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.
- Preventing rejects, scrap, and re-processing.
- Considering the possibility of real time release.
- Increasing automation to improve operator safety and reduce human error.
- Facilitating continuous processing to improve efficiency and manage variability
    - Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities.
- Improving energy and material use and increasing capacity.

The potential uses for PAT in Rottapharm Ltd. include the following:

- Confirm correct materials being used, reaction/blending completed e.g. Sachet Blending
- Remove need for Production to take samples for off-line analysis e.g. API Manufacture

It is evident from the potential gains of PAT outlined above, that a reduction in the number of deviations caused by human error would be

closely linked to an overall improvement in product quality and efficiency.

5.0 Summary and Conclusions

Retraining is a common corrective or preventative action to a PDR in Rottapharm Ltd. and in other similar pharmaceutical companies. While retraining sessions appear to be effective in the short-term, further medium- and long-term solutions must be found to address Human Error PDRs. Electronic process management systems (e.g. MES) and in-line testing can control and monitor processes, but for the foreseeable future, people will still control these systems.

Techniques to reduce levels of Human Error PDRs include 'mistake proofing', improvement of training manuals and department-wide and inter-department communication of PDR root causes to increase awareness and vigilance of issues. In addition, procedures, checklists and in-process checks can be implemented to train and guide personnel, and their performance can be monitored by second check reviews. These and other techniques can minimise Human Error PDRs, but they cannot eliminate them completely. When people are involved, the potential for Human Error PDRs to occur is a very real one that cannot be eliminated.

5.0 References

- EU GMP Volume 4 of "The rules governing medicinal products in the European Union", Part 1
- EU GMP Volume 4 of "The rules governing medicinal products in the European Union", Annex 20
- Rottapharm Ltd. Quality Policy – Quality Manual Section 05, Appendix 1
- Rottapharm Ltd. SOP QA-SYS-004, "The Process Deviation Reporting System"
- Rottapharm Ltd. SOP QA-SYS-009, "Change Control System"
- Rottapharm Ltd. SOP QA-SYS-010, "The Annual Product Quality Review"
- Rottapharm Ltd. SOP QA-SYS-015, "Internal Quality Auditing Programme"
- Rottapharm Ltd. SOP QA-SYS-061, "Risk Management Policy"
- Sachet Annual Product Quality Review Report, 2007 Rev. 01
- US FDA Guidance for Industry, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance", September 204

APPENDIX I

Appendix I

PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-001-S	Production	Sachets	Unsealed Sachet	Minor	P17M	Equipment Failure
PDR-06-004-S	Production	Sachets	Badly Cut Sachets	Minor	P2TM	Human error
PDR-06-005-S	Production	Sachets	Unsealed sachets	Major	P1DS	Equipment Failure
PDR-06-009-S	Production	Sachets	Unsealed Sachets	Major	P1DM	Equipment Failure
PDR-06-012-S	Production	Sachets	Unsealed Sachets	Major	P4NS	Unknown
PDR-06-013-S	Production	Sachets	Unsealed Sachets	Minor	P1NM	Equipment Failure
PDR-06-014-G	Logistics	Sachets	QA removed from Engineering Change Order (ECO) as an Approver	Major	L2DS	Human error
PDR-06-018-S	Production	Sachets	Unsealed Sachets	Major	P1ES	Equipment Failure
PDR-06-022-S	Production	Sachets	Unsealed sachets / Lumps in blend	Major	M4NS	Unknown
PDR-06-025-S	Production	Sachets	Unsealed Sachets	Major	P1DS	Equipment Failure

Appendix I

PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-026-S	Production	Sachets	Unsealed Sachets	Minor	P1DM	Equipment Failure
PDR-06-038-S	Production	Sachets	The agitator rod on the dosator on sachet filler SF102 seized and stopped	Major	P1DS	Equipment Failure
PDR-06-040-S	Production	Sachets	Defective lot of Foil	Major	P1NS	Equipment Failure
PDR-06-043-S	Production	Sachets	Unsealed Sachets	Major	P1DS	Equipment Failure
PDR-06-046-S	Production	Sachets	Badly Cut unsealed sachets	Minor	P1NM	Equipment Failure
PDR-06-047-S	Production	Sachets	Unsealed sachet	Major	P3ES	Material Quality
PDR-06-051-S	Production	Sachets	Badly cut sachet from SF102	Major	P3ES	Material Quality
PDR-06-054-S	Production	Sachets	Unsealed badly cut sachets	Major	P1TS	Equipment Failure
PDR-06-056-S	Production	Sachets	Incorrect batch number on Sachets from filler, SF102	Major	P2HS	Human error
PDR-06-057-S	Quality Assurance	Sachets	Duplication of batch numbers for secondary packaging of sub-batches	Major	P2HS	Human error

Appendix I

PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-058-S	Production	Sachets	Badly Sealed Sachet	Minor	P4NM	Unknown
PDR-06-060-S	Production	Sachets	Unsealed sachets	Major	P2HS	Human error
PDR-06-061-S	Production	Sachets	Badly Sealed Sachets	Major	P1NS	Equipment Failure
PDR-06-062-S	Production	Sachets	Damaged twin sachet and incorrect quantity of sachets in carton	Major	P1NS	Equipment Failure
PDR-06-067-S	Quality Control	Sachets	Weight issues with CGS Sachet Batch Z-60	Major	P4NS	Unknown
PDR-06-069-S	Quality Assurance	Sachets	BPR missing for batch	Major	Q2HS	Human error
PDR-06-071-S	Production	Sachets	Expiry date changed due to power down of machine	Major	P2DS	Human error
PDR-06-074-S	Production	Sachets	Unsealed Sachets found in P2	Minor	PINM	Equipment Failure
PDR-06-081-S	Production	Sachets	Seal test failures	Major	P3ES	Material Quality
PDR-06-083-S	Production	Sachets	Unsealed and badly cut sachets	Major	P3DS	Material Quality
PDR-06-087-S	Production	Sachets	Unsealed Sachets	Minor	P3NM	Material Quality

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PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-090-S	Production	Sachets	Unsealed sachet found during Bulk Packaging	Major	P1SS	Equipment Failure
PDR-06-095-S	Quality Control	Sachets	Weight Control Issues for sachet filler SF102	Major	P1HS	Equipment Failure
PDR-06-097-S	Production	Sachets	Screw found in carton at checkweigher reject station	Minor	P2HM	Human error
PDR-06-098-S	Production	Sachets	Unsealed sachet found in P1	Minor	P1HM	Equipment Failure
PDR-06-106-S	Production	Sachets	Badly Cut Sachet found in P1	Minor	P1ES	Equipment Failure
PDR-06-109-S	Production	Sachets	Badly sealed sachet from SF101	Major	P1HS	Equipment Failure
PDR-06-116-B	Production	Sachets	Wrong 'data de frabricaccao' on drum label	Minor	P5TM	System Error
PDR-06-117-S	Production	Sachets	Total batch weight following Dispensing OOS	Minor	M2HM	Human error
PDR-06-118-S	Production	Sachets	Badly Cut Sachets found at checkweigher	Major	P1HS	Equipment Failure
PDR-06-119-S	Production	Sachets	Unsealed Sachets found in P1	Major	P1ES	Equipment Failure

Appendix I

PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-121-S	Production	Sachets	Unsealed Sachet found in P1	Major	P4NS	Unknown
PDR-06-123-S	Production	Sachets	Unsealed sachets due to lumps in blend	Major	P4NS	Unknown
PDR-06-126-S	Production	Sachets	Incorrect Blending for sachet blends	Minor	M2HM	Human error
PDR-06-128-S	Production	Sachets	Unsealed Sachet in P2 from SF103	Major	P2TS	Human error
PDR-06-129-S	Quality Control	Sachets	Weight issues with batch	Major	P1ES	Equipment Failure
PDR-06-132-S	Technical Services	Sachets	The blender BL-102 screw would not rotate when blending was started	Minor	M1EM	Equipment Failure
PDR-06-134-S	Production	Sachets	Unsealed Sachet found in P1	Major	P4ES	Unknown
PDR-06-136-S	Production	Sachets	Badly Cut sachet found in P1	Major	P4ES	Unknown
PDR-06-137-S	Quality Control	Sachets	Unsealed Sachet found in QC Lab	Major	P3ES	Material Quality
PDR-06-144-S	Production	Sachets	Badly Cut sachet found in P2	Major	P1ES	Equipment Failure
PDR-06-145-S	Production	Sachets	Incorrect variable data on sachet from SF104	Major	P2ES	Human error

Appendix I

PDR Number	Originating Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-06-149-S	Production	Sachets	Unsealed sachets found at start up at batch	Major	P4ES	Unknown
PDR-06-151-S	Production	Sachets	Parts of sealing foam found in dosator filling Machine SF101	Critical	P1EC	Equipment Failure
PDR-06-152-S	Production	Sachets	Small rip in sachet	Major	P4ES	Unknown
PDR06-156-S	Production	Sachets	Badly cut Sachets	Major	P4NS	Unknown
PDR06-157-S	Production	Sachets	Badly Cut & unsealed sachets	Major	P4ES	Unknown
PDR-06-158-S	Production	Sachets	OOS Batch Yield	Minor	P2EM	Human error
PDR-06-160-S	Production	Sachets	Wrong blend utilized in batch	Minor	P2HM	Human error
PDR-06-161-S	Production	Sachets	Screw found in carton at reject station	Minor	P2HM	Human error

Total No. PDRs	**159**
Total No. Sachet PDRs	**59**

2 cancelled

APPENDIX II

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-001-S	Production	Sachets	Badly cut sachets found at reject station	Major	P1NS	Equipment Failure
PDR-07-003-S	Production	Sachets	Unsealed sachet found in F1 due to unequal seal at top of sachet	Minor	P1HM	Equipment Failure
PDR-07-004-S	Production	Sachets	Incorrect price on carton	Major	P2DS	Human Error
PDR-07-005-S	Production	Sachets	Unsealed sachet due to lump of powder found in funnel	Major	P4ES	Unknown
PDR-07-008-S	Production	Sachets	Unsealed sachet found in P2	Major	P1DS	Equipment Failure
PDR-07-010-S	Production	Sachets	De-laminating of foil on filler SF104	Major	P4NM	Unknown
PDR-07-011-S	Production	Sachets	Problem with flow of blend casuing erratic weights	Major	P4NS	Unknown
PDR-07-017-S	Production	Sachets	During a routine check QA discovered that the expiry date on the sachet foil and the expiry date on the cartons where different	Major	P2HS	Human Error
PDR-07-019-S	Production	Sachets	Badly cut sachet found in P2	Major	P1ES	Equipment Failure
PDR-07-024-S	Production	Sachets	Unsealed Sachet found in P2	Major	P4DS	Unknown
PDR-07-025-S	Production	Sachets	Unsealed sachets due to lumps in blend	Major	P4DS	Unknown

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-027-S	Production	Sachets	Badly cut sachet found in P1	Major	P1ES	Equipment Failure
PDR-07-028-S	Production	Sachets	Badly cut sachets found in F1/P1	Major	P1ES	Equipment Failure
PDR-07-029-S	Production	Sachets	Unsealed sachets - lumps in blend	Major	P4ES	Unknown
PDR-07-033-S	Production	Sachets	Unsealed sachets found P2	Major	P4NS	Unknown
PDR-07-034-S	Production	Sachets	Badly cut sachets found P1/F1	Minor	P1DM	Equipment Failure
PDR-07-037-S	Production	Sachets	Small rip found in sachets in P1 from SF101	Major	P4ES	Unknown
PDR-07-041-S	Production	Sachets	Incorrect Expiry date used	Minor	P2HM	Human Error
PDR-07-042-S	Production	Sachets	Unsealed sachets found P1/F1	Major	P4ES	Unknown
PDR-07-043-S	Production	Sachets	Unsealed sachets on SF103 found in F2/P2	Major	P4ES	Unknown
PDR-07-044-S	Production	Sachets	Badly cut sachet found in P1 and F1	Major	P1ES	Equipment Failure
PDR-07-046-S	Quality Control	Sachets	Weight control and content assay issues	Minor	Q3NM	Material Quality
PDR-07-049-S	Production	Sachets	Unsealed sachets found P2	Major	P4ES	Unknown

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-050-S	Production	Sachets	Unsealed sachets SF102 found F1/P1	Major	P1ES	Equipment Failure
PDR-07-051-S	Production	Sachets	Unsealed sachets from SF103 & SF104 found F2/P2	Major	P4ES	Unknown
PDR-07-052-S	Production	Sachets	Unsealed sachets on SF101 and SF102 -F1/P1	Major	P4ES	Unknown
PDR-07-053-S	Production	Sachets	Unsealed sachets found P1	Major	P4ES	Unknown
PDR-07-055-S	Production	Sachets	Unsealed sachets	Major	P4ES	Unknown
PDR-07-058-S	Production	Sachets	Missing Variable data on catons	Major	P2ES	Human Error
PDR-07-061-S	Production	Sachets	Unsealed sachets found in P2/ Badly cut sachets found in P2	Major	P1ES	Equipment Failure
PDR-07-062-S	Production	Sachets	Unsealed sachets found P1/F1	Minor	P2EM	Human Error
PDR-07-063-S	Production	Sachets	Badly cut sachets found in P1	Minor	P7EM	Design Limitations
PDR-07-064-S	Production	Sachets	Unsealed sachets SF102	Minor	P3SM	Material Quality
PDR-07-067-S	Production	Sachets	Unsealed sachet	Major	P4ES	Unknown
PDR-07-068-S	Production	Sachets	Variable data missing from carton	Major	P2HM	Human Error

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-069-S	Production	Sachets	Unsealed sachets found in P2	Minor	P4ES	Unknown
PDR-07-070-S	Production	Sachets	Unsealed Sachets found	Major	P1ES	Equipment Failure
PDR-07-071-S	Production	Sachets	Variable data print missing on carton	Major	P2HS	Human Error
PDR-07-072-S	Production	Sachets	Unsealed sachets found in F2/P2	Major	PINS	Equipment Failure
PDR-07-073-S	Production	Sachets	Unsealed sachets found in F2/P2	Major	PIDS	Equipment Failure
PDR-07-074-S	Production	Sachets	Unsealed sachets found in F2/P2	Major	P4ES	Unknown
PDR-07-075-S	Production	Sachets	Unsealed Sachets Found from SF104	Major	P4ES	Unknown
PDR-07-078-S	Production	Sachets	Badly cut Sachets found in P1/F1 at the reject check weigher	Major	P7ES	Design Limitations
PDR-07-079-S	Production	Sachets	unsealed sachets found by operator at the checkweigher station P2	Major	P4ES	Unknown
PDR-07-083-S	Production	Sachets	Unsealed, badly sealed and tares on sachets	Major	P4ES	Unknown
PDR-07-084-S	Production	Sachets	Unsealed Sachets found in F1	Major	P4ES	Unknown
PDR-07-085-S	Production	Sachets	Unsealed found in F1on conveyor belt	Major	P1ES	Equipment Failure

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-086-S	QA	Sachets	Some IP checks omitted	Minor	P2TM	Human Error
PDR-07-087-S	Production	Sachets	Partially filled sachets found in P2	Major	P1ES	Equipment Failure
PDR-07-089-S	Production	Sachets	Internal liner of CGS FIBC damaged	Major	M7DS	Design Limitations
PDR-07-091-S	Production	Sachets	Variable data from the code block were to be printed on cartons with ink but ink roller was not present on machine	Minor	P2HM	Human Error
PDR-07-094-S	Production	Sachets	Badly cut sachets found in P1 at checkweigher	Major	P4ES	Unknown
PDR-07-097-S	Production	Sachets	Badly cut Sachets	Major	P4ES	Unknown
PDR-07-098-S	Production	Sachets	Badly cut sachets found in P1 from SF102	Major	P4ES	Unknown
PDR-07-103-S	Production	Sachets	Incorrect expiry date on cartons	Major	P2HS	Human Error
PDR-07-104-S	Production	Sachets	Unsealed sachets found in P2/ F2	Major	P3ES	Material Quality
PDR-07-110-S	Production	Sachets	Unsealed sachets found in P1 from SF102	Major	P2ES	Human Error
PDR-07-113-S	Production	Sachets	Badly cut sachets SF102	Major	P4ES	Unknown
PDR-07-116-S	Production	Sachets	Fragment of blue nitrate glove found in Comil mill after dispensing of CGS batch 07297	Major	M2HS	Human Error

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-119-S	Production	Sachets	Badly cut sachet found in P2 SF014	Major	P4ES	Unknown
PDR-07-121-S	Production	Sachets	Badly Cut Sachets	Major	P1ES	Equipment Failure
PDR-07-123-S	Production / TS	Sachets	Pieces of nylon based cable found in Comil sieve after dispensing of CGS IRL 07237	Major	M2HS	Human Error
PDR-07-126-S	Production	Sachets	Unsealed sachets found on SF104 and later on SF103	Major	P3ES	Material Quality
PDR-07-127-S	Production	Sachets	Unsealed sachets found in rejection station in P2	Minor	P3ES	Material Quality
PDR-07-128-S	Production	Sachets	Badly cut sachets found on line 1	Major	P1HS	Equipment Failure
PDR-07-129-S	Production	Sachets	Badly cut sachets found on line 1 SF101	Major	P4ES	Unknown
PDR-07-132-S	Production	Sachets	Unsealed Sachet found in outer in P2	Major	P4ES	Unknown
PDR-07-133-S	Production	Sachets	Missing print on carton	Minor	P1DM	Equipment Failure
PDR-07-137-S	Production	Sachets	Part broken of cartoner	Minor	P1EM	Equipment Failure
PDR-07-138-S	Production	Sachets	Badly cut sachets and unsealed sachets found in P2	Major	P4ES	Unknown

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-140-S	Production	Sachets	Badly cut / torn sachets and pinched sachets from SF101	Major	P1HS	Equipment Failure
PDR-07-141-S	Production	Sachets	Torn sachet found while carrying out IP check	Major	P1ES	Equipment Failure
PDR-07-143-S	Production	Sachets	Badly cut sachets on SF103 SF104	Major	P4ES	Unknown
PDR-07-144-S	Production	Sachets	Badly cut sachets found in P2	Major	P1NS	Equipment Failure
PDR-07-145-S	Production	Sachets	Unsealed sachet found in P1 / F1	Major	P2ES	Human Error
PDR-07-147-S	Production	Sachets	Rip and sticky (wet) stain on sachet from SF104	Major	P4ES	Unknown
PDR-07-148-S	Production	Sachets	Unsealed sachet found in P1	Major	P2ES	Human Error
PDR-07-149-S	Production	Sachets	Unsealed sachets found in P2	Major	P1DS	Equipment Failure
PDR-07-151-S	Production	Sachets	Torn sachet found in P1	Minor	P1EM	Equipment Failure
PDR-07-154-S	Production	Sachets	Badly cut sachets from SF104	Major	P1ES	Equipment Failure
PDR-07-155-S	Production	Sachets	Badly cut sachets from SF103	Major	P4ES	Unknown

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-156-S	Production	Sachets	A small length of wire was found in the comill during a routine inspection	Major	M1HS	Equipment Failure
PDR-07-158-S	Production	Sachets	Torn sachet found in carton in P2 and unsealed Sachets found	Major	P1ES	Equipment Failure
PDR-07-159-S	Production	Sachets	Unsealed sachets found in SF104	Major	P1ES	Equipment Failure
PDR-07-161-S	Production	Sachets	Unsealed sachets found along the perforation of twinned sachet from SF104	Major	P1ES	Equipment Failure
PDR-07-164-S	Production	Sachets	Unsealed sachet found in P1	Major	P2ES	Human Error
PDR-07-166-S	Production	Sachets	CGS over-dispensed, Vacuum transfer failure	Minor	M7HM	Design Limitations
PDR-07-170-S	Production	Sachets	Badly cut sachets found from SF103	Major	P4ES	Unknown
PDR-07-173-S	Production	Sachets	Unsealed sachets found in P2	Minor	P1ES	Equipment Failure
PDR-07-175-S	Production	Sachets / blend	Metal particles found in Comil on completion of dispensing of GS 07541	Major	M1ES	Equipment Failure
PDR-07-176-S	Production	Sachets	Unsealed and badly cut sachets found in P2	Major	P4ES	Unknown
PDR-07-178-S	Production	Sachets	Badly cut sachet found in P1 from SF101	Minor	P2ES	Human Error
PDR-07-182-S	Production	Sachets	Unsealed Sachets found in F2 P2	Major	P4ES	Unknown

Appendix II

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-07-186-S	Production	Sachets	Batch blended for 1 hour instead of 30 mins	Major	M2HS	Human Error

Total No. PDRs	**187**
Total No. Sachet PDRs	**93**

APPENDIX III

Appendix III

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-008-S	Production	Sachets	Unsealed sachets found in P1 from Sf101	Major	P4ES	Unknown
PDR-08-014-S	Production	Sachets	Badly cut sachets found in P2	Major	P1ES	Equipment Failure
PDR-08-015-S	Quality Control	Sachets	The print error occurred causing the batch number to be illegible	Minor	P1HM	Equipment Failure
PDR-08-017-S	Production	Sachets	Unsealed sachet found in P1 from SF102	Major	P4ES	Unknown
PDR-08-024-S	Production	Sachets	Suction cup causing damage to Sachet	Major	P1ES	Equipment Failure
PDR-08-025-S	Production	Sachets	Badly cut sachet P2	Major	P1ES	Equipment Failure
PDR-08-026-S	Quality Assurance	Sachets	Incorrect DOM on cartons	Minor	P2HM	Human Error
PDR-08-028-S	Production	Sachets	Unsealed sachet found in F1/P1 and screw found in carton	Major	P2ES	Human Error
PDR-08-029-S	Production	Sachets	Badly cut sachet found in P1	Major	P3ES	Material Quality
PDR-08-030-S	Production	Sachets	Torn sachet from SF101 in P1	Minor	P1EM	Equipment Failure
PDR-08-032-S	Production	Sachets	Incorrect setting on checkweigher	Minor	P2TM	Human Error

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-039-S	Production	Sachets	Unsealed sachet found in P1	Major	P1ES	Equipment Failure
PDR-08-040-S	Production	Sachets	Badly cut sachet found in P2	Major	P1ES	Equipment Failure
PDR-08-041-S	Production	Sachets	Badly cut sachet from Sf101 found in P1	Major	P1ES	Equipment Failure
PDR-08-043-S	Production	Sachets	Badly cut sachets SF102	Major	P1ES	Equipment Failure
PDR-08-044-S	Production	Sachets	Badly cut sachets SF101 / SF102	Major	P1ES	Equipment Failure
PDR-08-045-S	Quality Control	Sachets	Low out of specification result for the glucosamine assay.	Major	M4NS	Unknown
PDR-08-048-S	Production	Sachets	Badly sealed sachets found in P2 at start up of batch	Major	P4ES	Unknown
PDR-08-049-S	Production	Sachets	Badly cut sachets found in P1 F1from SF101	Major	P1ES	Equipment Failure
PDR-08-050-S	Production	Sachets	Checkweigher rejects not falling into reject bin	Minor	P1EM	Equipment Failure
PDR-08-052-S	Production	Sachets	Badly cut sachets & unsealed sachet from SF101	Major	P4ES	Unknown

Appendix III

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-053-S	Production	Sachets	Badly cut sachets found from SF102	Major	P1ES	Equipment Failure
PDR-08-054-S	Production	Sachets	Unsealed sachets found from filling machines SF101 & SF102	Major	P4ES	Unknown
PDR-08-057-S	Production	Sachets	Badly cut sachets found in P1	Major	P1ES	Equipment Failure
PDR-08-058-S	Production	Sachets	Badly cut sachets found in P2	Major	P1ES	Equipment Failure
PDR-08-061-S	Quality Control	Sachets	OOS content assays obtained	Minor	P1ES	Equipment Failure
PDR-08-063-S	Production	Sachets	Unsealed Sachet found in P2 from SF104	Major	P1ES	Equipment Failure
PDR-08-067-S	Production	Sachets	Batch was short sachets to finish	Minor	P1EM	Equipment Failure
PDR-08-069-S	Production	Sachets	Badly cut & unsealed sachets found in P1	Minor	P1ES	Equipment Failure
PDR-08-070-S	Production	Sachets	Badly cut sachet found in P1	Major	P1ES	Equipment Failure
PDR-08-071-S	Production	Sachets	Trials carried out during batch	Minor	P2TM	Human Error
PDR-08-079-S	Production	Sachets	Unsealed Sachets found in P1	Major	P2HS	Human Error

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-080-S	Production	Sachets	Full cleans of room M8 are due every 7 days. The Full clean of the room was not completed until 14 days had elapsed.	Minor	M2HM	Human Error
PDR-08-081-S	Production	Sachets	Batch was dispensed and blended as a 2400kg blend	Major	M2HS	Human Error
PDR-08-085-S	Production	Sachets	Badly cut sachets from SF 102 found in P1	Major	P1ES	Equipment Failure
PDR-08-086-S	Production	Sachets	Wrong CGS used in Sachet Blend S08198	Major	M2HS	Human Error
PDR-08-088-S	Production	Sachets	Screw found in carton	Minor	P1EM	Equipment Failure
PDR-08-089-S	Production	Sachets	Unsealed Sachets found in P2 (SF103)	Major	P1EM	Equipment Failure
PDR-08-092-S	Production	Sachets	Area clearance for rooms M8 and M9 not signed off	Minor	M2TM	Human Error
PDR-08-095-S	Production	Sachets	OOS Yield and OOS Reconciliation	Minor	M2HM	Human Error
PDR-08-096-S	Production	Sachets	Badly cut sachet found in P1	Major	P4ES	Unknown
PDR-08-097-S	Production	Sachets	Wrong amount of PEG 4000 dispensed into blend S08251.	Minor	M2HM	Human Error
PDR-08-098-S	Production	Sachets	Punctured sachets from FI	Minor	M1EM	Equipment Failure

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-099-S	Production	Sachets	Hoist chain fell into bag of CGS	Major	M1ES	Equipment Failure
PDR-08-100-S	Production	Sachets	Incorrect identification label	Minor	Q2HM	Human Error
PDR-08-104-S	Production	Sachets	Badly cut sachet found in P2	Major	P4ES	Unknown
PDR-08-107-S	Production	Sachets	Unsealed sachets	Major	P2ES	Human Error
PDR-08-108-S	Production	Sachets	Unsealed Sachets	Major	P4NS	Unknown
PDR-08-109-S	Production	Sachets	Unsealed sachets and metal stud found in carton	Major	P1ES	Equipment Failure
PDR-08-110-S	Production	Sachets	Badly Cut sachet found in P1	Minor	P2EM	Human Error
PDR-08-112-S	Production	Sachets	Badly cut sachets SF101/SF102	Major	P4ES	Unknown
PDR-08-113-S	Production	Sachets	Two incidents of Unsealed sachets found in P2	Major	P2NS	Human Error
PDR-08-115-S	Production	Sachets	Damaged carton with torn sachet passing into case-packer	Minor	P1EM	Equipment Failure
PDR-08-120-S	Quality Control	Sachets	Sachets from filler SF103, 25% contained cutting error. Dosator number missing.	Minor	Q2TM	Human Error
PDR-08-121-S	Quality Control	Sachets	Expiry date illegible on sachet box	Minor	P4EM	Unknown

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-124-S	Production	Sachets	Unsealed sachets found in P1	Minor	P4EM	Unknown
PDR-08-125-S	Production	Sachets	Unsealed sachet due to obstruction in Funnel.	Minor	P2HM	Human Error
PDR-08-126-S	Production	Sachets	Incorrect batch number issued for Dona 4's bulk sachets	Minor	Q2TM	Human Error
PDR-08-128-S	Production	Sachets	Torn sachet leading to leaking powder	Major	P1ES	Equipment Failure
PDR-08-132-S	Production	Sachets	Wrong expiry date on sachets from filler SF103	Minor	P2HM	Human Error
PDR-08-133-S	Production	Sachets	Badly cut sachet found in P1	Major	P1ES	Equipment Failure
PDR-08-134-S	Production	Sachets	Badly cut sachet found in P1	Major	P1ES	Equipment Failure
PDR-08-135-S	Production	Sachets	Badly cut sachet found on SF101 and SF102	Major	P1ES	Equipment Failure
PDR-08-137-S	Production	Sachets	Badly cut sachets	Minor	P2HM	Human Error
PDR-08-138-S	Production	Sachets	Unsealed sachet due to vibration control valve not opening fully	Major	P1ES	Equipment Failure

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PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-143-S	Production	Sachets	The requirement for the * to be printed on sachets from SF103 for Clinical Trials batches is not necessary.	Major	P2HS	Human Error
PDR-08-144-S	Production	Sachets	Tech working in F2 on sealing plate issues. The sealing plates on SF103 would not close due to a pin out of place.	Minor	P2DM	Human Error
PDR-08-146-S	Production	Sachets	Badly Cut sachet found in P1	Minor	P4EM	Unknown
PDR-08-149-S	Quality Control	Sachets	Black marks were found on Sachets from batch B-75	Major	P2ES	Human Error
PDR-08-150-S	Production	Sachets	Unsealed Sachets from Filler SF104	Minor	P1HM	Equipment Failure
PDR-08-151-S	Quality Assurance	Sachets	No second checks on dispensing	Minor	M2HM	Human Error
PDR-08-152-S	Production	Sachets	Unsealed Sachet found in P2 at the checkweigher	Major	P1ES	Equipment Failure
PDR-08-153-S	Production	Sachets	Smudged print on variable code on sachets from SF103	Minor	P2EM	Human Error
PDR-08-156-S	Production	Sachets	Badly cut sachet from SF101 found in P1	Major	P1ES	Equipment Failure
PDR-08-157-S	Engineering	Sachets	Under dispensing of Plantago Ovata into the blend	Major	M2HS	Human Error

Appendix III

PDR Number	Department	Product Type	Brief Description	Category	Classification	Primary Root Cause
PDR-08-163-S	Production	Sachets	Torn sachet from SF102 found in P1	Major	P1SS	Equipment Failure
PDR-08-164-S	Production	Sachets	Badly cut sachet from SF101	Major	P1NS	Equipment Failure

Total No. PDRs	**163**
Total No. Sachet PDRs	**77**

1 cancelled