CHAPTER 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

Cleaning validation in pharmaceutical testing facilities complying with Good Manufacturing Practices (GMP) has been a contentious subject for many years. The manufacturer must demonstrate that the cleaning procedure used will consistently minimise the probability of product adulteration which ensures the quality, purity and safety of a given drug product. The question thus exists if the testing laboratory, as an extension of the manufacturing plant also needs to comply with this requirement (Patel & LoBrutto, 2007).

It is important to maintain and care for laboratory equipment as it is an integral part of the analytical method. All laboratory equipment must be cleaned according to specific methods and protocols. Of particular interest is the importance of laboratory glassware in pharmaceutical laboratories where testing and/or calibration forms part of inspection and product certification. Laboratory glassware is an essential tool of generating data in the pharmaceutical industry and has a crucial effect on the quality of tested final products (Salo *et al.*, 2008). Testing of finished products in pharmaceutical laboratories is a measure of the quality of drugs manufactured. This process is of essence to ensuring that drugs or medicines made available to the public are safe, efficacious and are of the right quality standard for their intended health use (Wrigley, 2004).

Glass is a common material encountered in laboratories which for many applications is the ideal material of choice for laboratory apparatus and containers due to its chemical inertness, temperature durability, and cleanliness (Hanlon & Ramiń, 1999). Soda lime, borosilicate and quartz are three commonly glass materials used to manufacture laboratory glassware. Borosilicate, sometimes called "hard" glass is the most popular due to its ability to withstand temperatures of up to 230°C (Hanlon & Ramiń, 1999). Glassware such as burettes, volumetric flasks and pipettes are calibrated to accurately

measure or deliver specific volumes of chemicals during an analysis and are subject to multiple uses especially in laboratories where glassware use is non-dedicated (Boca *et al.*, 2005). The random use of glassware in a laboratory requires glassware free of contamination; otherwise, these contaminants may cause interferences that could adversely affect reproducibility of results (Schmerber *et al.*, 2005) .

Possible adulteration sources are previously tested products, cleaning agents, solvents, and the water utilised during the cleaning cycle of the equipment. A glassware cleaning procedure should hence consistently remove residues of the substance previously tested down to levels that are deemed acceptable (Nozal *et al.*, 2000) and should itself not contribute unacceptable levels of residual material to the glassware (APIC, 1999). A cleaning procedure should have the ability to remove any cleaning agents introduced during cleaning after the cleaning process is completed (Resto *et al.*, 2007). The acceptance criteria for the residual-cleaning agents should reflect the absence of these materials, within a range of the capabilities of the assay and sampling methods (APIC, 1999). According to APIC (1999), each individual company must decide on the acceptance criteria which are justifiable for their particular situation.

The active pharmaceutical ingredients (API) and the detergent are two dynamics that need to be analysed for cleaning verification (Patel & LoBrutto, 2007). Since residual amounts of the API and the detergent are to be determined, the assay method needs to be very sensitive. For measuring the API, the assay of the content uniformity method can be employed. If the sensitivity of the assay method is not acceptable, then modifications can be made to an existing method or a more sensitive test method can be developed (Patel & LoBrutto, 2007). Methods for determining the detergent or detergent residues poses to be more challenging since no official methods exist.

It is necessary to validate cleaning procedures for it is a customer requirement in ensuring the safety and product purity (APIC, 1999). Validation assures an internal control and compliance to quality but most importantly it is a regulatory requirement stipulated in the cGMP (Resto *et al.*, 2007). Validation is the medium with which

compliance to GMP and cGMP guidelines is attained and presented in a systematic way (Gibson & Powell-Evans, 1998). Validation mandates documentation of scientific studies conducted to prove that a protocol can consistently be used to generate comparable quality results under predetermined acceptable specifications. Validating prompts the appraisal of every activity involved in a pharmaceutical process and almost inevitably entails proper recording and communication.

Good manufacturing practices (GMP) are official governmental publications (Gibson & Powell-Evans, 1998) regulating the proper manufacturing of pharmaceutical products that are safe, efficacious and are of high quality standard for public health use (Wrigley, 2004). GMP regulations emphasizes that quality, safety and efficiency must be designed and built into the entire manufacturing and production process of raw and finished products (Wrigley, 2004). Current good manufacturing practices (cGMP) are federal regulations emphasizing that the expectations for compliance are dynamic, compliance with cGMP is not a static situation, but requires the manufacturer to be aware not only of what is current in the industry but also of innovations that may be good (Wrigley, 2004). GMP and "cGMP" are internationally the fundamental quality controlling aspects of almost if not all pharmaceutical laboratories.

Coordinating uniformity of rules and regulations amongst pharmaceutical laboratories worldwide eliminates barriers and gives way to trade in pharmaceutical products. It is therefore of outmost importance to measure and to ensure that pharmaceutical laboratories do not only comply with GMP and cGMP but can prove the validity of the products manufactured and laboratory generated data. When GMP is carried into every step of product testing or manufacturing, it gives all interested parties a day-to-day assurance that quality is not compromised, product corruption is minimized, and the opportunity to trace the source of discrepancies is maximized (Gibson & Powell-Evans, 1998).

This study focuses on a third party pharmaceutical laboratory where testing of pharmaceutical products mainly form part of post importation release, inspection and

quality control. In this particular laboratory glassware use is non-dedicated. Results generated in this laboratory are very critical to the quality of medication to be consumed by patients not only in South Africa but the whole Africa and neighbouring continents.

1.2 HYPOTHESIS

Laboratory glassware has been identified as a potential risk of contamination in pharmaceutical contract testing laboratories. Testing of pharmaceutical products requires the use of clean glassware at all times to assure the validity and quality of the results generated in a laboratory. A glassware cleaning procedure should consistently remove residues of the substance previously tested down to levels that are deemed acceptable (Nozal *et al.*, 2000) and should itself not contribute unacceptable levels of residual material to the glassware (APIC, 1999).

High Performance Liquid Chromatography (HPLC) will be used in this study to help illustrate and characterise representative approaches to real situations in order to accentuate the significance of clean laboratory glassware use. HPLC coupled with UV detection will be used to monitor the efficiency of glassware cleaning methods due to its high sensitivity, selectivity, automation characteristics, and ability to detect compounds with low UV chromophores (Boca *et al.*, 2005).