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ORIGINAL RESEARCH

Bioequivalence Common Deficiencies in Generic Products Submitted for Registration to the South African Health Products Regulatory Authority (SAHPRA)

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Abstract

Background The cost of healthcare has become expensive globally, of which the greater part of the money is spent on buying innovator medicines. In order to make medicine affordable, the development of generic medicines has become paramount. The science of bioequivalence studies of generic products to demonstrate therapeutic equivalence with innovator products has been developed over the last 50 years. These studies cost far less as compared to innovator products thereby reducing the cost of medicines. Accelerating access to medicines has become an increasing challenge due to insufficient resources from regulatory authorities, while pharmaceutical industry continues to expand. An investigation on the deficiencies identified during scientific assessments by SAHPRA in submitted bioequivalence studies is therefore paramount. Identification and publication of these deficiencies will assist in accelerating the access of medicines to patients.

Objective The aim of the study is to investigate the types and frequency of the common deficiencies observed in the bioequivalence section of generic submissions to SAHPRA. The study was conducted retrospectively over a 7-year period (2011–2017) for generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. A more recent analysis on common deficiencies witnessed for applications assessed between 2020 and 2021 was also done to illustrate the consistency in the evaluation practises adopted by SAHPRA.

Methods There were 3148 applications finalised between 2011 and 2017, and to attain a representative sample for the study, statistical sampling was conducted. The multi-stage sampling called stratified systematic sampling was selected as the method of choice. The sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation resulting in the selection of 325 applications (Fig. 2a). Additionally, 300 master applications were assessed between 2020 and 2021 for up-to-date data (Fig. 2b). All the deficiencies were collected and categorised according to the ICH E3 guideline and components relevant to biostudies.

Results A total of 2458 deficiencies were collected from the selected sample size for applications finalised between 2011 and 2017 where a biostudy was submitted. The majority of the identified deficiencies were from the following categories; in vitro dissolution testing and specifications (18%), study design (17%), details on the test and reference products (16%), issues on sample analysis (16%), and statistical analysis (10%) (Fig. 3). From the applications assessed in 2020–2021, 492 deficiencies were identified with a similar trend compared to those finalised between 2011 and 2017. Comparison of the deficiencies with those reported by the USFDA and WHO PQTm is discussed with similarities outlined.

Conclusions The five most common deficiencies observed were extensively discussed. The outcomes of this study will guide pharmaceutical companies, sponsors, and Clinical Research Organisations (CROs) in submitting quality biostudies which will reduce turnaround times for registration and accelerate access to medicines for patients. In addition, the deficiencies identified will assist assessors from the different regulatory authorities to improve on their bioequivalence assessment.

Keywords South African Health Products Regulatory Authority (SAHPRA) · Common deficiencies · Bioequivalence · Bioavailability · Biostudies · Generic products

Introduction

Innovator pharmaceutical products are New Chemical Entities (NCEs) that have received a patent on the chemical formulation or manufacturing process and obtained registration

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from a regulatory authority after extensive testing [1]. Innovator and generic products are both available on the market, but innovator products are usually more expensive compared to the generics due to extensive research conducted from discovery and development to marketing and promotion of the product [2]. For example, clinical trials which are the primary tool to assess safety, efficacy and clinical benefits of new Finished Pharmaceutical Products (FPPs) in humans tend to be time consuming, expensive, and burdensome for subjects. These can be replaced by the cost-saving bioequivalence studies which ensure the progression of future therapeutic development. In 2017 alone, the United States of America (USA) government was able to save $265.1 billion due to the use of generic products, and an overall of $1.67 trillion was saved in the last decade [2]. In South Africa, the domestic manufacturing pharmaceutical industry almost exclusively produces generic products, and the South African pharmaceutical sector is import dependent [3]. In 2013, generic medicines accounted for 63% of the private pharmaceutical market and 80% of the market share in the South African government's pharmaceutical use [3].

Bioavailability refers to the rate and extent to which the Active Pharmaceutical Ingredient (API), or its active moiety, is absorbed and becomes available at the site of action [4]. When two formulations of the same API or two FPPs are claimed bioequivalent, it is expected that they are therapeutically equivalent [4–8]. The generic products submitted to regulatory authorities must be both pharmaceutically equivalent and bioequivalent to the corresponding innovator product to establish that the two products are therapeutically equivalent. A biowaiver may also be requested instead of submission of the biostudies, when justified, in line with the Biopharmaceutics Classification System (BCS) [7] .

The South African Health Products Regulatory Authority (SAHPRA) receives approximately 1200 applications per annum from pharmaceutical companies for registration into the market, and 90% of these are generic products. Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice, as these trials tend to be insensitive to formulation differences and usually require a very large number of patients [7]. Further, these studies in humans can be financially limiting, often unnecessary and may be unethical [5]. As a result, the science of bioequivalence testing has been developed over the last 50 years [7].

Data from biostudies are received and evaluated by the Pharmaceutical Evaluations and Management (PEM), Pharmaceutical and Analytical (P&A) pre-registration Unit. SAHPRA mostly relies on external evaluators to execute biostudy evaluations. The P&A pre-registration Unit utilised five to eight external experts as biostudy evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provide the necessary support to the Unit and the meetings served as a quality assurance measure for all products. Committee members provide technical and scientific advice for evaluations in the pre-registration Unit. This meant that each biostudy report on the evaluation of the data provided in the dossier was discussed in the meeting before it can be communicated to the applicant. Due to the resultant backlog of applications over the years, SAHPRA embarked on a project called the Backlog clearance programme aimed at clearing the existing backlog over a specified time. Inherited processes and practices from the former Medicine Control Council (MCC) were re-assessed, and the backlog project was initiated to support new methodologies required to achieve the goal of clearing the backlog of applications [9]. All applications received by SAHPRA prior to February 1, 2018 were considered to be part of the backlog project and ~ 8000 applications were in the pre-registration phase [9]. The authority, therefore, implemented a process that allows applicants to re-submit the dossiers, as some information may be required to be updated since the backlog applications were initially submitted as far back as 2008. Re-submission windows (RW) were created based on the importance of therapeutic categories of medicines to the country. Re-submission window one (RW1) consisted of medicines in the therapeutic category of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Vaccines and Hepatitis, while re-submission window two (RW2) was for medicines in the therapeutic category, oncology medicines [10]. Re-submission window five (RW5) was for medicines targeting Diabetes, Malaria, maternal and newborn health as well as all the priority APIs [10]. The inclusion of the backlog applications in this study is to identify the biostudy deficiencies and establish if there are any differences in the outcomes from the newly developed biostudy assessments practices.

The four major study report components for biostudies and evaluations are as follows: in vitro dissolution testing, bioanalytical validation and analysis, clinical study reports, and details of the test and reference products used as illustrated in Fig. 1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) E3 guideline provides the structure and content of the clinical study reports [11]. In an effort to improve the quality of biostudy submissions by the applicants, different regulatory authorities developed additional guidelines [4–8]. The United States Food and Drug Administration (USFDA) published guidance documents on General Bioavailability and Bioequivalence (BA/BE) Guidance [6], Statistical Approaches to Bioequivalence Guidance [12], and creation of the online Dissolution Methods Database (November 2005) to name a few. The USFDA noted that although there has been an improvement in the overall quality of the submissions with the employment of the guidelines and the Dissolution Methods Database

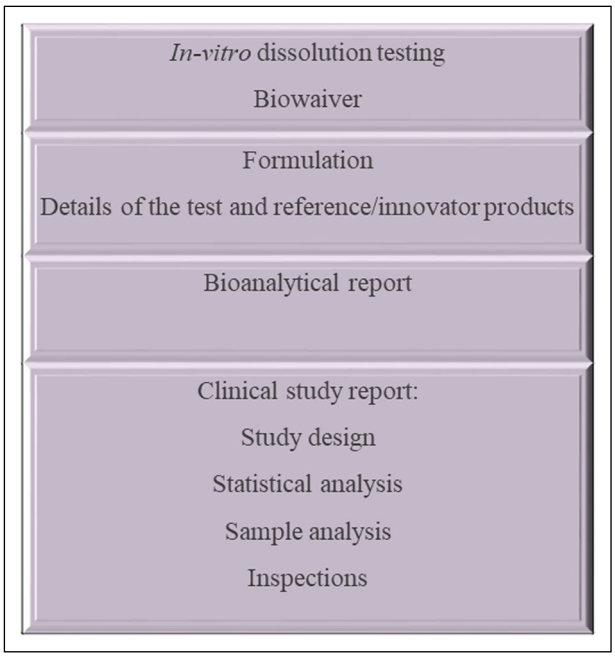

Fig. 1 Four groups of bioequivalence study components with nine categories for the deficiencies observed in biostudy submissions

[13], there were still some recurring deficiencies that may be associated with one or more of the components of the biostudy reports of the applications. This resulted in authorities publishing common deficiencies observed in biostudy evaluations to the industry in order to avoid future delays in submissions and promote access of medicine to patients. Thus far, reports on common deficiencies were published by the USFDA [14] and the World Health Organisation Prequalification Team: Medicines (WHO PQTm) [15]. This current study therefore aims to identify and quantify common deficiencies in the biostudy section of generic products finalised by SAHPRA's PEM pre-registration Unit between 2011 and 2017. In addition, deficiencies identified in applications assessed between 2020 and 2021 were also investigated. The transparency between the authority and industry on common deficiencies in the biostudy section will assist in reducing the scientific review process and thereby accelerating the access of medicines to patients.

Method

Over the 7-year period (2011–2017), 3148 applications were finalised by the P&A pre-registration Unit within SAHPRA. The sterile products (667), Veterinary (68), Biologicals (86), Medical Devices (5), and New Chemical Entities (NCEs) (233) were also finalised by the P&A Committee in the period as shown in Fig. 2 but were not included as part of this study. NCEs require the submission of clinical trial data assessed by the Clinical Evaluation Unit within SAHPRA. Solutions for oral use, aqueous solutions administered by parenteral routes, powders for reconstitution, otic, ophthalmic, nasal, topical, and cutaneous products containing the API in the same molar concentration as the reference product are considered to be equivalent without further documentation of equivalence [5]. The applicant should demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product [5]. Sterile products are normally classified in the above dosage forms, thus, biostudies are not required and not submitted for these. The biological products also use sterile preparations due to the criticality and nature of the active moiety. The veterinary products were not included in the study since the P&A Committee only provided support to the veterinary Unit on each application in terms of quality assessments only. The veterinary applications require the submission of clinical trial data due to the diversity across animal species' physiology and the numerous dosage forms used in veterinary practice resulting in unique formulations and dosage routes [16]. As such, technical requirements for registration of veterinary medicines are constantly evolving as a result of scientific developments [16]. Lastly, medical devices were not included in this study because the sample size was too small to render the deficiencies common.

The distribution clearly shows that SAHPRA receives a large number of generic products since 90% of the finalised products are generic products and 66% of those are non-sterile (Fig. 2a).

Due to the large population size of the non-sterile products, a statistical sampling method became a requirement for this research. The sample selected needs to be a true representation of the population, and the results of the study can be generalised to the population as a whole. Selection of the sampling method is crucial as different sampling techniques are used for specific research problems since one technique may not be appropriate for all problems [17]. The sample size determination and sample selection for the non-sterile products have been well described in the findings on common deficiencies in the Active Pharmaceutical Ingredient section by SAHPRA [18]. Stratified systematic sampling is the selected sampling method, and a sample size of 325 non-sterile applications was obtained (Fig. 2a) [18].

For the study investigating applications assessed between 2020 and 2021, all applications received in re-submission windows one, two, and five (300) (Fig. 2b) where a

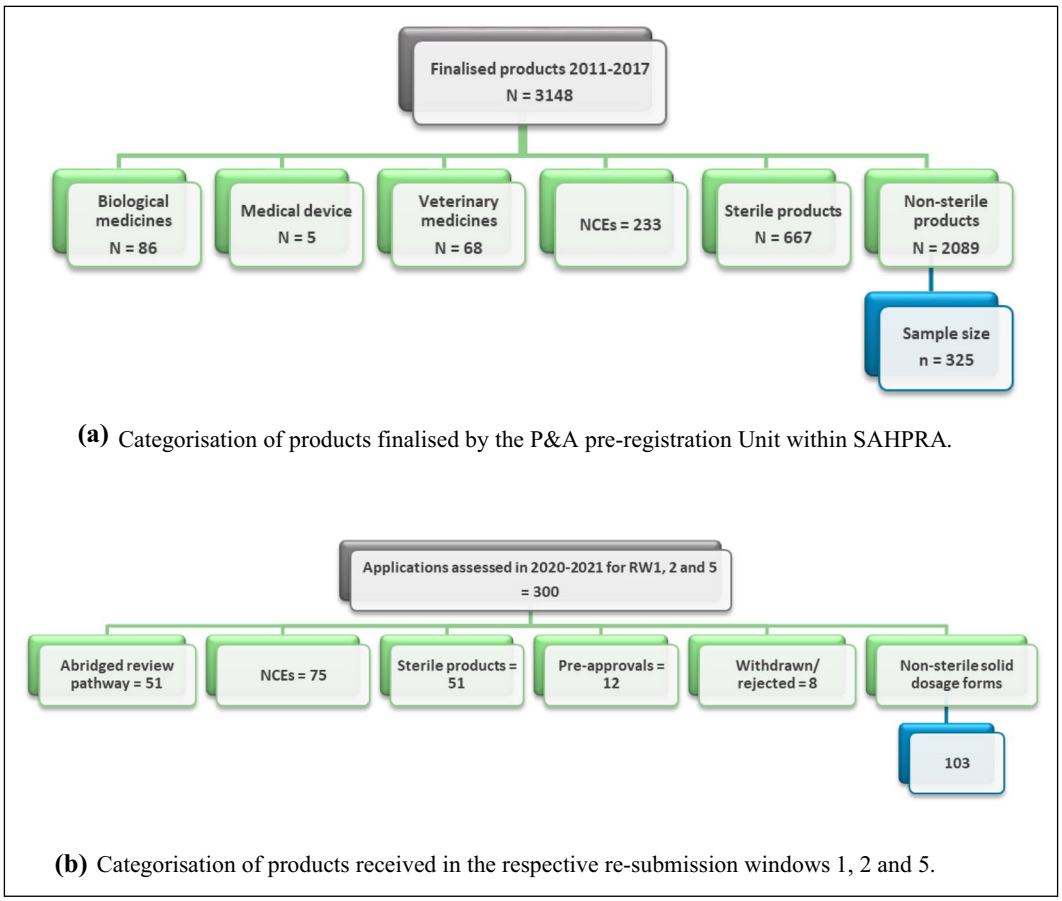

Fig. 2 **a** Categorisation of products finalised by the P&A pre-registration Unit within SAHPRA. **b** Categorisation of products received in the respective re-submission windows 1, 2 and 5

biostudy was submitted were used. An overall of 84 (RW1), 143 (RW2), and 73 (RW5) applications were received in the respective windows. Table 1 and Fig. 2b illustrate the distribution of the pathways the applications undertook in the three windows. Abridged review pathway is an external reliance mechanism employed by the authority wherein reports from other authorities are received and comparison of the scientific content conducted instead of full scientific review. In addition, there were applications that were pre-approved by the PEM before the 1st of February 2018, these have been assessed and finalised by the Unit previously although not yet registered. Lastly, the first two windows consisted of NCE submissions as these are high priority and require the submission of clinical trial data. Thus, biostudy

Table 1 The illustration of applications received in re-submission windows 1, 2 and 5

	Re-submission window 1 (RW1)	Re-submission window (RW2)	Re-submission window (RW5)
Total applications received	84*	143*	73*
Abridged review pathway	8	22	21
Liquid dosage forms (biostudy not required)	5	29	17
Non-sterile solid dosage forms (biostudy required)	31†	48†	24†
Pre-approvals (already assessed)	1	4	7
NCEs	39	36	–
Withdrawn/rejected	–	4	4

*Total number of applications received in each category

†Total number of non-sterile applications in each RW with biostudies, used in the study

submissions were for a total of 103 applications between the three windows.

Collection of Deficiencies

The full history of all the products finalised between the 7-year period (2011–2017) was collected which comprises of all communication between the authority and applicants in order to reach finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses in the form of amendment schedules. These paper documents were obtained from the committee meeting minute documents and the registry files where all documents relating to the product are placed. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during the multiple rounds of communication. For applications assessed between 2020 and 2021, the full history was obtained in the electronic database for SAHPRA applications. The deficiencies in the initial query letters were collected and quantified. The selected nine categories for the deficiencies are as illustrated in Figs. 1 and 3.

The deficiencies obtained were reviewed and the frequency of each biostudy component was listed with the percentage frequency calculated as follows:

- Percentage frequency of deficiency identified per biostudy component = (frequency of specific deficiency/Total number of deficiencies biostudy component) × 100.

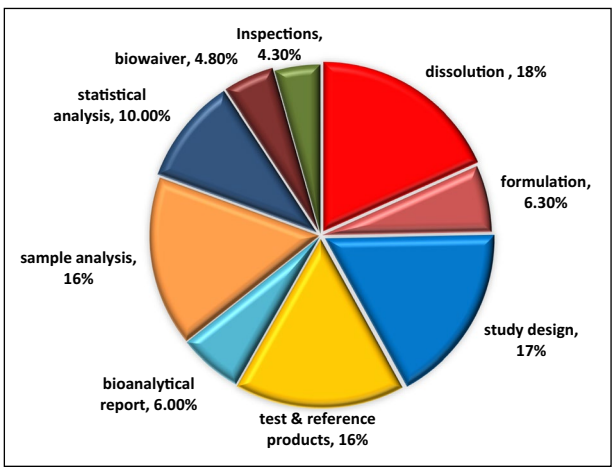

Fig. 3 Distribution of deficiencies from biostudies finalised between 2011 and 2017 by the PEM pre-registration Unit

All charts, graphs, and analyses were carried out with Microsoft Office Excel® 2016 (Microsoft Corporation, USA).

Results

From the stratified systematic sampling, a sample size of 325 non-sterile applications was obtained, and of those, nine were non-sterile products which do not require the submission of a biostudy such as oral liquids, topical products, etc., classified under "other" as indicated in the types of dosage forms below. The applications contained a variety of solid dosage forms, which are film-coated and uncoated immediate-release tablets, (48%), immediate-release capsules (23%), orodispersible tablets (8.0%), extended-release tablets (8.0%), extended-release capsules (3.5%), chewable tablets (1.2%), powders for suspensions (5.1%), and other (3.2%). There was an overall of 2458 deficiencies collected from the 316 initial letters from the biostudy sections.

For the applications assessed between 2020 and 2021, there were 103 applications where a biostudy was submitted as outlined in Table 1. Of the 103, 50 were film-coated and uncoated immediate-release tablets (49%), 25 were immediate-release capsules (24%), 10 were powders for suspension (13%), eight were extended-release tablets and capsules (10%) and other (4.0%). This is a similar trend of the types of dosage forms received between 2011 and 2017 as indicated above. There were 492 deficiencies obtained as stipulated and discussed in the following section.

The deficiencies observed in the four components are expanded on in Tables 2, 3, 4 and 5.

Discussion

Figure 3 clearly depicts the distribution of the deficiencies observed in the biostudies. It shows that the highest deficiencies, 18%, were from dissolution testing. This component is followed by study design (17%), queries on the test and reference products (16%), sample analysis (16%), and statistical analysis (10%). The common deficiencies observed in the categories are further discussed below.

In Vitro Dissolution Testing and Biowaivers

Dissolution testing is an essential part of product development and serves as a quality control measure once the composition and the manufacturing process are defined for the scale-up of production batches to ensure batch-to-batch consistency [5, 6, 19–22]. It is also used in support of a biowaiver of bioequivalence testing to demonstrate the similarity between different product formulations of an active

Table 2 List of common deficiencies observed in in vitro dissolution testing and biowaivers identified by SAHPRA between 2011 and 2017

Deficiencies In vitro dissolution testing	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
Comparative dissolution studies must be conducted per the requirements in the guideline to include the purpose of study, products batch information, full dissolution conditions, and method validation, as well as numbers of units per the study, how units were filtered, and any problem with pH related stability of the samples should be indicated and discussed in terms of preventative handling measures, analysis and interpretation of data, analytical method or reference to part of the dossier, results (API dissolved): tabulated, graphically, similarity determination/f2 calculation if necessary	64	15	2
The calculation of similarity factor values (f2) for profiles is not appropriate and should be corrected	13	2.9	
The calculation on the similarity factor for the two profiles was not conducted and should be submitted	10	2.3	
The submitted individual dissolution data are not accepted. There should be 12 units used for the comparative dissolution studies between the test and reference products	21	4.8	5
Include the dissolution data for the innovator reference product (foreign and/or South African) as this was not submitted	15	3.4	
Bring the final product release and stability dissolution specifications in Module 3.2.P.5.1 in line with the profiles of the biostudy test (and reference) products. A specific specification is proposed based on the results observed	33	18	33
The dissolution profiles in the selected quality control medium were not included and should be submitted	30	6.8	19
Describe the method for withdrawal and filtration of samples and how this ensures that dissolution of non-dissolved particles does not occur after sampling Include in-line filtration for drawing the dissolution samples in the dissolution method in 3.2.P.5.2 to ensure that the dissolution of the sample is stopped immediately on withdrawal of the sample (USP "Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary"). If the method states that the samples should be drawn and filtered this does not necessarily imply or ensure that the dissolution of undissolved particles in the sample is stopped at the time of sampling	46	11	19
Demonstrate the similarity of the dissolution profiles of the reference and corresponding test product or SA innovator in three of the physiological media and justify the use of other buffers apart from those in the guideline or the addition of a surfactant	30	6.8	4
The sample withdrawal times and other aspects do not comply with the requirements stipulated in the dissolution guideline	29	6.6	
Provide a statement on whether in vivo and in vitro correlation from the data were obtained	09	2.0	
Indicate where the dissolution studies were conducted as well as the dates when the studies were conducted	10	2.3	6
The submitted dissolution data are incomplete for the extended-release products as it is lacking dissolution data in multimedia and alcohol dose dumping data for extended-release products	10	2.3	
Consider including an additional dissolution specification for the extended-release products with a longer release rate	06	1.4	
Demonstrate the discriminatory nature of the dissolution method in 3.2.P.2 to ensure that it is sensitive to changes in manufacturing processes and /or in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters	59	13	24
Other	09	2.0	
	442		112
Biowaiver			
Provide evidence to show the proportional similarity of the different strengths. Fully address biowaiver requirements for the lower strength(s) by including confirmation that all strengths are manufactured using the same process, similar equipment, similar dissolution profiles, linear pharmacokinetics, etc	38	32	15
The BCS classification of the API has not been identified and all requirements according to the guideline regarding the appropriateness of the BCS biowaiver have not been addressed, evidence that the API is fully absorbed upon oral administration is also required	31	26	

Table 2 (continued)

Deficiencies In vitro dissolution testing	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
According to pharmacopoeial monograph, the API is poorly soluble and poorly permeable therefore BCS II/IV. Therefore, the API will not be considered by SAHPRA for biowaiver			10
Provide permeability studies to confirm the indicated BCS classification of the API	41	34	5
A biowaiver for the additional strength cannot yet be granted until data for dissolution at pH 1.2 is also provided, or the omission justified			10
For a BCS-based biowaiver application, comparison should have been demonstrated for each strength of the test product with the corresponding strength of the foreign reference product. In addition, the following documentation for the reference products should have been submitted: a. Copies of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate b. Copies of the comparator products carton outer boxes. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling c. Copies of CoAs for the comparator products			3
A volume of 1000 ml was used for the dissolution comparative dissolution studies for biowaiver purposes. This volume may be acceptable for release testing; however, this is not acceptable for biowaiver purposes. You should submit new comparative dissolution data in 900 ml of media (pH 1.2, 4.5 and 6.8) and at release conditions			6
Other	09	7.6	
	119		49

substance and the reference medicinal product and to indicate potential problems with bioavailability. Thus, issues regarding comparative dissolution details between the test and reference products used in the biostudy are assessed in this component as well as the appropriateness of the proposed dissolution specifications.

For biowaivers, the Biopharmaceutics Classification System (BCS) waiver is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the API and is intended to reduce the need for in vivo bioequivalence studies [21]. This is confirmed by comparison of the proportional additional strength(s) and similarity of the dissolution profiles in the three physiological media with the reference product [4, 5]. The deficiencies observed in the biowaiver requests are therefore investigated in this component.

The dissolution of a product is important for its bioavailability and therapeutic effectiveness and is therefore considered a critical parameter in biostudies [23]. The deficiencies observed in these components are listed in Table 2, and Fig. 4 further highlights the five most frequent deficiencies observed in the sections. Dissolution testing requires the development of a robust and rugged dissolution method that is adequately discriminating to distinguish any changes that could affect the product [22, 23]. As depicted on Table 2, there was 13% of deficiencies relating to the discriminatory nature of the selected dissolution method not having been demonstrated and was therefore requested. The choice of an adequate medium that can discriminate between critical manufacturing variables is crucial in such cases [24, 25]. The changes may include quantitative formulation, material specifications, and/or using slightly modified process parameters [25] .

When a dissolution test is not defined in the monograph of the product, or if the monograph is not available, a comparison of product dissolution profiles is recommended in three different dissolution media at physiological pH ranges, that is, 0.1 N Hydrochloric acid—pH 1.2, Acetate buffer—pH 4.5 and phosphate buffer—pH 6.8 [21, 22]. Table 2 clearly shows that there were 6.8% of these deficiencies from the dissolution testing category. If the API is poorly soluble, appropriate concentrations of a surfactant are recommended, and therefore, comparative dissolution results should also be submitted in the selected medium with the surfactant [21]. A clearly described justification is required for these products since this is not encouraged. The comparative dissolution study results should be submitted in accordance with the SAHPRA dissolution guideline which is in the three media as described above, specified dissolution vessel, media volume and agitation speed between the test product and reference product [24, 26, 27], there were 15% of the deficiencies requesting this. The 15% also comprised of deficiencies such as lack of submission of the method validation, inadequate numbers of units used for performing the study, how the units were filtered, similarity determination (f2) calculation

Table 3 List of common deficiencies in the bioequivalence clinical study reports identified by SAHPRA for non-sterile products finalised by the pre-registration Unit between 2011 and 2017

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
3.0. Include a comprehensive table of contents (ToC) for the Overview. General information guideline 3.1.2 and Biostudies guideline 3.9. (currently not relevant since SAHPRA allows only electronic submissions)	30	7.1	
5.1. Submit the ethical approval letter by the Ethics Committee or Institutional review board (IRB) for the approved protocol and the subject consent forms	26	6.1	
9.1. The meal composition employed in fed studies should be consistent with the description in the labelling i.e. Profession Information (PI)	23	5.4	
9.1. The Summary of product characteristics (SmPC) of the reference product indicates that the product should be taken with food, therefore submit the appropriate biostudy i.e. fed study	09	2.1	
9.1. Justify the inclusion / explain/clarify the relevance and appropriateness of the proposed pharmacokinetic information in the professional information with reference to the results of the bioequivalence study, by a comparison of the results (including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs). Copies of these references should be provided as well). The submitted fasting study does not appear to support the pharmacokinetic values for plasma concentration in the proposed PI, and no statement regarding the effect of food on the bioavailability of the final product is included	09	2.1	2
9.1. Evidence of food effect must be included for fed studies. Alternatively: The biostudy employed an open label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study in healthy adult male human subjects under fed conditions, because the comparator product in the European Union is taken with food. However, the claim that it can be taken with and without food requires that the biostudy should be conducted in fasting conditions	34	8.0	13
9.2. Include the complete dates of the treatment schedules, ensure that the washout period is not excessively larger than five times the largest expected half-life	32	7.5	
9.3.1/2. The inclusion and exclusion criteria could not be located in the protocol	14	3.3	
9.4.5 The proposed sampling times are found inadequate and not sufficient to cover the Cmax	10	2.4	
9.4.5 Provide clarity on the dates of the study reports and analytical reports	27	6.4	
9.4.5 The lowest Cmax is at a specified time based on the submitted concentration–time data. This means that there is only one post dose time point before the Cmax. Provide evidence to show that no Cmax happened between the 1st sampling time and the lowest Cmax			2
9.7.2. Ensure that the number of additional subjects added to the sample size to compensate for potential dropouts or withdrawals are realistic and consistent with the study design	12	2.8	
9.7.2. Provide the parameters and method that were used to determine the sample size	25	5.9	
9.7.2. Provide justification for the proposed sample size as it is lower than the minimum requirement	12	2.8	
10.2. Insufficient information provided on the protocol e.g. address deviations in the submitted and approved protocol	35	8.2	
14.1. Submit individual subjects' demographic profiles i.e. age, race, ethnicity, gender, and body mass	25	5.9	9
14.1. Submit the number of females and males participating in the study	25	5.9	
16.1.1. Provide the protocol for the study which includes the protocol final version number	19	4.5	
16.1.1. The protocol should indicate the software that will be used for the statistical calculations and factors to be included in the Analysis of Variance (ANOVA) should be well defined	24	5.6	
16.1.2 Confirm that case report forms will be available upon request or for inspection. (this is now a requirement by SAHPRA, case report forms should be included in the submissions) 2011–2017	21	4.9	
16.1.2 Provide copies of Case report forms (CRFs) completed at screening for the volunteers recruited for inclusion in the fasting study. A blank copy of the CRF was found in 16.1.2 for all studies, this is noted but not adequate to address this requirement. 2020–2021			2

Table 3 (continued)

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
16.1.2 Tabulate the respective laboratory results against the normal ranges for any results that were outside of study site normal values. Further, the case report form for respective study participants must also be provided			4
Other	13	3.1	
	425		32
Sample analysis			
9.5.4. Provide the temperature of the water bath in which the samples were defrosted before testing	46	11	
9.5.4. Demonstrate the long-term stability of the plasma samples in the study under the correct study conditions for the period between centrifuging and analysis	59	15	20
9.5.4. Provide a description of the sample transportation, transport temperature recording from the clinical site to the analytical site	39	9.7	10
9.5.4. Provide or justify why no definitive time, temperature, and speed is given for the centrifuging of samples after receiving the blood samples	25	6.2	15
9.5.4 Calibration data, i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters, for the entire study should be provided	11	2.7	7
12.2. Provide a discussion on the selection of samples for repeat analyses as these could not be located	15	3.7	5
12.2 Provide the SOP specifying the criteria for reanalysis and reporting of reanalysed samples			2
12.2. Plasma samples from subjects who dropped out or were withdrawn due to an adverse event should be analysed for a complete safety analysis of the data	31	7.7	
14.2. Submit 20% of chromatograms in accordance with the SAHPRA biostudies guideline 3.9.2.e. The chromatograms must have a table of contents indicating the subject and page numbers. The legend or sample coding system must be included and clearly identified and sampling time given	76	19	10
14.2. Submit the mean and all individual plasma concentration versus time profiles presented on a linear/linear as well as log/linear scale	40	10	9
14.2 Provide evidence that the analytical method used was able to detect and resolve the primary analyte from possible metabolites			3
14.2 A discussion of sensitivity in terms of signal-to-noise ratio determined at Lower limit of quantification (LLOQ) concentrations including the signal-to-noise ratio values should be provided for the methods used to analyse the APIs in the plasma			4
14.2. Provide legible concentration vs time plots and Certificates of Analysis (CoAs)	29	7.2	8
14.2. Submit complete documentation with respect to subject sample analyses	26	6.5	6
Note that samples from all dosed subjects should be analysed for safety evaluation			20
Other	06	1.5	
	403		119
Statistical analysis			
11.4.1. Comment on the high standard deviation (SD) of the area under the curve (AUC)	25	9.9	
11.4.1. The submitted pharmacokinetic/statistical calculations are incorrect and require revision and re-calculation	27	11	
11.4.1. The criteria for selection of samples for reanalysis are not objective, unscientifically sound or potentially biassed towards a favourable bioequivalence outcome. Provide adequate justification for the selection of samples used for reanalysis	19	7.5	
11.4.1. The biostudy submission consists of missing data files required for statistical analysis. Submit the missing data files	12	4.7	
11.4.1. Indicate how sampling deviations were handled in the statistical analysis	11	4.3	
11.4.1. Correct/justify the statement in the PI under pharmacokinetic properties where it is stated that peak plasma is reached after a specified time, while data presented in the biostudy show peak plasma is reached well within a different time	19	7.5	
11.4.1. Address and justify for the high point estimates that have been obtained on the results	21	8.3	

Table 3 (continued)

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
11.4.1. Provide a justification of the extended bioequivalence criteria of 80–125%	22	8.7	
14.2. Provide adequate justification for subjects that are excluded from the statistical analysis	48	19	
14.2 The matrix effect should be evaluated by analysing at least 3 replicates of low- and high-quality controls (QCs), each prepared using a matrix from at least 6 different sources/lots. The accuracy should be within ± 15% of the nominal concentration and the precision (percent coefficient of variation (%CV)) should not be greater than 15% in all individual matrix sources/lots as per International Council for Harmonisation (ICH) acceptance criteria			11
14.2 Provide the complete statistical software printouts of the analysis made on log transformed data for AUC0-t and Cmax to help justify your findings reported in the ANOVA table			4
14.2 The statistical output of Statistical Analysis Software (SAS) system in appendix 16.1.9.2 does not include the calculation of the 90% Confidence interval (CI) for the ratio test/reference of the primary pharmacokinetic parameters when the conventional ANOVA with subject, sequence, period, and subject (sequence) factors are analysed. Provide new statistical analysis including the raw SAS output taking into account the recommendations above			8
14.2. Submit the calculated point ratios of the AUC0-t, AUC0-inf, and Cmax	23	9.1	
16.1.11. Provide a discussion of the study results with available literature references	12	4.7	10
Other	14	5.5	
	253		33
Inspections			
16.1.8 Provide a GMP/GLP compliance declaration by the laboratory, including reference to the availability of validation records of test methods and procedures for and records of calibration of instruments and maintenance of equipment	24	23	
16.1.8 Provide auditing and monitoring activities that took place in relation to the studies undertaken	25	24	15
16.1.8 Confirm that the Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including participant files are available for verification by the Inspectorate and indicate the facility where all the relevant study documentation is available for inspection by the Good Clinical Practice (GCP) inspectors	47	44	10
16.1.8 Submit a declaration that all the biostudy documents are available for inspection by the Inspectorate and indicate the facility at which they may be inspected	17	16	7
Provide the executed Batch Manufacturing Records (BMR) for the biobatch used in the biostudy			9
Ensure that the Bioequivalence Trial Information Form (BTIF) is adequately and accurately completed to reflect the same data as on the submitted dossier			15
Ensure that all documents are adequately bookmarked with appropriate titles/document names			10
Other	10	9.4	
	106		66

where necessary. The complete list of deficiencies for this component is included in Table 2. In the case where the reference product used in the biostudies is not procured in South Africa (SA), SAHPRA requires a comparative dissolution study report between the foreign reference product and the SA innovator product to confirm equivalence [21]. The results of the biostudy test product are therefore used to determine the dissolution specification for the product in Module 3.2.P.5.1. The deficiency where an incorrect or unacceptable dissolution specification is proposed (18%) for the final product is very common and leads to the back and forth communication between the applicants and the authority thus delaying registration. The dissolution specifications should be based on the results of the biostudy test product since the manufacturer needs to ensure that the manufacture of the proceeding batch continues to meet the standard of the biostudy test product. If the product is unable to meet these specifications in the stability results, it illustrates the deterioration of the quality of the product which should therefore be addressed by

Table 4 Common deficiencies witnessed in aspects relating to the reference and test product including formulation comparisons

Deficiencies Formulation	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
Confirm that the formulation being applied for is the same as that of the biostudy test product. The data should include unit formula, manufacturing procedure, equipment, site of manufacture, source of raw material, overall product specifications, and other relevant information	41	26	6
Provide a comparison of the qualitative formulation of the test and reference products	21	13	2
Provide justification for the major differences observed in the formulation for the test and reference products	22	14	
For studies five years and older, submit data to confirm that the product being applied for is identical to the test product used in the bioequivalence study. The data should include but not be limited to the following: •Unit formulation, manufacturing procedure, and equipment •Site of manufacture of final product and manufacturer of the API •Overall product specifications and •Other relevant information	67	42	6
Other	07	4.4	
	158		14
Details of the reference and test products			
Provide a justification for the use of the biostudy reference product fully complying with the requirements stipulated in the SAHPRA guideline	48	12	5
The potency and/or content uniformity data for the test product were not submitted	33	8.5	
Provide further literature information to support the proposed reference product	13	3.4	
Provide a justification for the proposed batch size, which is smaller than the recommended batch size in accordance to the biostudy guideline	33	8.5	6
Provide detailed CoAs for the biostudy reference and the corresponding innovator product in South Africa which include the dissolution, assay, and impurity results	13	3.4	20
Evidence to show that the reference product used in the study is equivalent to the innovator product registered by SAHPRA must be submitted	54	14	4
Submit the corrected complete overview 3.2.R.1 according to the guideline	25	6.4	
The biostudy test batch and that used in the validation and stability batches are from two different manufacturing sites. The equivalence or essential similarity of the two products manufactured by the stated final product manufacturers has not been adequately addressed and is not accepted. Demonstrate essential similarity between the product manufactured by manufacturer 1 and the product manufactured by the final product manufacturer being applied for, i.e. manufacturer 2	15	3.9	
Provide certified copies of invoice/ purchase documents as proof of receipt of the reference product and South African (SA) innovator product used in the bioequivalence study as well as copies of immediate container label and carton which visibly includes the name of the product, name and address of the applicant, batch number, and expiry	19	4.9	2
The shipment and storage of the reference product should be submitted and properly documented	34	8.8	6
Ensure and confirm that the final product release and stability specifications for total impurities are in line with the impurity profile of the reference product	19	4.9	
Batch size, manufacturing date (test product), and expiry date of the biostudy reference and test products must be included	39	10	
Submit CoAs of the foreign reference and the SA innovator products	33	8.5	
Other	10	2.6	14
	388		57

investigating the product development. The justification of changing the dissolution specification based on the stability results is therefore not acceptable.

Dissolution testing can also be used to support the bioavailability of a new pharmaceutical product in which case a biowaiver is requested. The frequent deficiency on the

Table 5 Deficiencies observed by SAHPRA on the bioanalytical report submitted for the bioequivalence studies

Deficiencies Bioanalytical report issues	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
The bioassay validation report must be submitted	12	8.2	
Submit the analytical method report and bioanalytical method standard operating procedure (SOP) which could not be located	36	25	10
Submit the detection and quantification limits of the parent and metabolites of the analytical methods	34	23	
The biological matrix used was not clearly indicated in the report	12	8.2	
The reasons for the high rate of failures of control samples could not be located. This should be justified	23	16	
Provide a discussion of the preparation of the calibration curve standards and the quality control samples	20	14	
Other	10	6.8	
	147		10

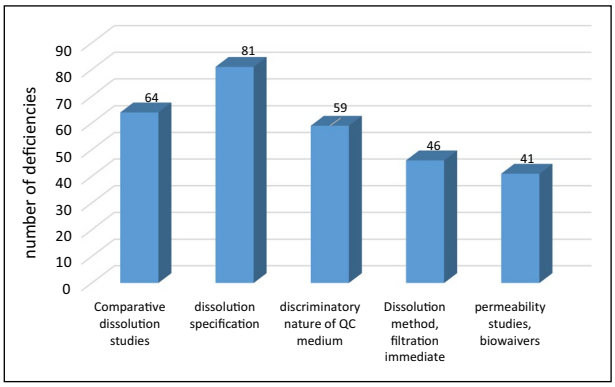

Fig. 4 Distribution of the five highest deficiencies observed in the in vitro dissolution testing and biowaivers section

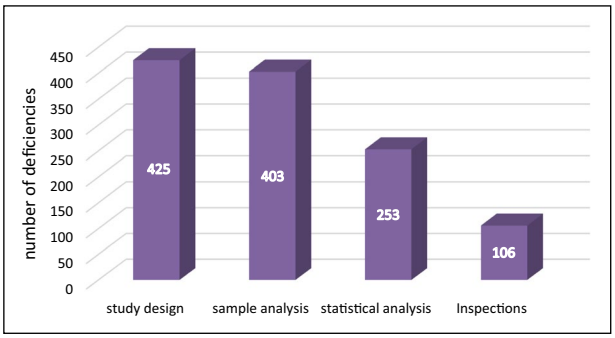

Fig. 5 Categorisation of the deficiencies in the bioequivalence clinical study reports

biowaivers was on the request of permeability studies to confirm BCS class I or III. Class I and III APIs are considered highly soluble, while Class II and IV have low solubility. With regard to permeability, Class I and II have high permeability, while III and IV have low permeability. Thus, when a BCS-based biowaiver is requested, it is imperative to support the classification of the API with solubility and permeability studies.

Clinical Study Reports

The conduction of bioavailability studies in humans requires that the FPP be administered to a group of individuals and that the time-course of the concentration of the API in the blood be evaluated [28]. The clinical study reports provide a summary of this scientific data. The clinical study report section is divided into four sub-categories based on the common deficiencies observed. These are further described in detail below and the quantification is depicted in Table 3 and Fig. 5.

Study Design

Study design involves the adequacy and appropriateness of the bioequivalence study design selected covering aspects such as the following:

Selection and appropriateness of single-dose, multiple dose or steady-state studies.
Selection and appropriateness of a two-period, two-sequence, crossover design or a parallel design.
Appropriateness and acceptability of the dose selected to conduct the biostudy.
Selection and appropriateness of the study selected to investigate food effects, if relevant, thus whether under fed or fasting conditions depending on the molecule and medicine under investigation.

Acceptability of the number of subjects proposed to conduct the study.

The study design selected for 91% of the 316 applications was simple single-dose, randomised, two-treatment, two-period, crossover biostudies. The most common experimental plan for comparing the bioavailability of two products is a simple crossover study as outlined above [5–8]. In this design, each individual in a group of subjects receives both FPPs at different times so that there is a direct comparison of the absorption of each product in the same individual. Special care must be taken to allow sufficient time to elapse (washout period) between the administration of the first and second final product so that there are no carryover effects [5]. In order to minimize the influence of such effects on the outcome of the study, good experimental design requires that each final product be administered initially to half of the subjects, hence this being the most common study design selected. There are however special cases where this study design cannot be employed depending on the behaviour of the API under investigation, in such cases a different study design such as parallel design, steady-state studies, multiple dose studies are selected [5]. The study design deficiencies as depicted in Table 3 included deviations witnessed in the protocol which differ from the approved protocol (8.2%). The protocol should be approved by a reputable ethics Committee or Institutional Review Boards (IRB) before the study commences, should there be any amendments or deviations to the protocol these should also await approval by the Committee. The deficiencies noted were not stated in the approved version of the protocol, and therefore, the latest protocol was required. Other deficiencies also involved applicants not including the Ethics approval letter (6.1%). Ethical approval is an integral part of the research process and aims to protect both researchers and participants who should have enough details to make informed and autonomous decisions [29]. The details on the study design also did not include critical aspects such as demographic details of the subjects i.e. age, race, ethnicity, body mass and description of the gender of subjects used in the study (12%), the inclusion and exclusion criteria employed (3.3%), and instances where an incorrect study has been included between the fed- and fasting study (7.5%). If the reference product's labelling instruction includes that the product should be taken with food or an extended-release product is applied for, a fed study should be submitted [30] .

Sample Analysis

The third component with the highest deficiencies is sample analysis comprising 16% as seen in Fig. 3 with the deficiencies listed in Table 3. This covers issues observed relating to the sample analysis procedure such as the appropriateness of the sample collection and sampling times selected, stability of the plasma sample, assurance that the Clinical Research Organisation (CRO) follows Good Clinical Practice in the sample collection and storage, and appropriateness of the bioanalytical analysis of the samples [5] .

The most frequent deficiencies in the Sect. (41.9%) are on sample handling before the analysis. This is a critical aspect in biostudies since during storage the final product may undergo chemical degradation, adsorption on the walls of the container, etc., thus, storage of plasma samples is important [5, 6]. Complete information on the long-term stability data of the samples was either not included or insufficient (15%), or details on the transportation and transport temperature recordings of the sample from the clinical site to the analytical site (9.7%), or the details of centrifugation of the blood samples (6.2%) or the details of the treatment of the frozen samples before testing (11%) were not provided. These are critical parameters that need to be safeguarded and adequately documented to ensure that the quality of the samples is maintained throughout the biostudy. Other deficiencies witnessed include the submission of chromatograms which should be 20% of consecutive subjects involved in the study. There was also a deficiency observed on the request to analyse samples for subjects who initiated the study and dropped out or were withdrawn due to adverse events (7.7%). This remains a requirement in order to obtain a complete safety analysis.

Statistical Analysis

This involves assessment of the issues associated with the statistical calculations of the pharmacokinetic parameters used to deduce bioequivalence. The statistical method for testing relative bioavailability is based on the 90% confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. The pharmacokinetic parameters should be analysed using statistical software called Analysis of variance (ANOVA) to attain an acceptance criterion for the main bioequivalence [4, 5]. The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80–1.25 (80–125%) for the investigated parameters in order to confirm bioequivalence.

Deficiencies in statistical analysis accounted for 10% of the biostudies investigated. The most common deficiency was from the lack of justification for the exclusion of subjects from the statistical calculation which constituted 19%. It is important to include the results of all subjects that were dosed from the study to avoid bias. The calculation of the pharmacokinetic (PK) parameters should be accomplished from observed data instead of fitted data. Some deficiencies included incorrect calculations on the PK parameters noted

by the evaluator which required correction. These constituted 11% of the deficiencies in the category.

For the biostudy to be established, 90% confidence interval for the ratio of the geometric least-square means of peak plasma concentration, AUC of test, and reference products should be within 80–125%. [5, 24, 31] Closer limits are considered for products that have a narrow therapeutic index, serious dose-related toxicity, steep dose effect curve, and nonlinear pharmacokinetics within the therapeutic dose range. European guidelines also provide a tightened acceptance interval of 90.00–111.11% for narrow therapeutic index drugs (NTIDs) as well as highly variable products which SAHPRA has adopted [24, 31]. A wider acceptance range is admissible if it is based on a sound clinical justification [6]. This justification was not included in some biostudies submitted with the extended range (10%) and this was requested.

Inspections

Deficiencies on inspection reports of the CRO conducting the biostudy as well as any outstanding audit and monitoring reports for the biostudy are required in order to confirm that the biostudy was conducted in line with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) requirements. Confirmation that the sponsor, investigational sites, facilities, laboratories, all data (including source data), documentation and reports concerning the biostudy including participant files must be available for verification by the Inspectorate Unit. This was queried and comprised of 44% of the deficiencies in this section as illustrated in Table 3. Over and above the biostudy information being submitted to the authorities, it is critical that the raw and complete data sets for the study be archived for the Inspectorate Unit to request upon inspections.

Aspects Relating to the Reference and Test Products

One of the critical aspects in selecting a reference product is ensuring that the assay content and dissolution data are similar to the test product. For example, the assayed content of the batch used as a test product should not differ by more than 5% from that of the batch used as the reference product [7]. Acceptability of the source of the reference product is also assessed, this should be sourced from an authority SAHPRA aligns itself with, thus all supporting documentation and testing of the test and reference product should be included [5]. Deficiencies relating to outstanding documentation or details regarding the test, foreign reference, and SA innovator product were investigated in this component.

The common deficiencies in this category as highlighted in Table 4 include the request to justify the proposed reference product in accordance with biostudy guidelines and available decision trees on the selection of the appropriate reference product. These comprised 12% of the deficiencies identified in this category. In the case where the reference product is not procured in SA, the following supporting information on the foreign reference product is required:

- The name and address of the manufacturing site where the reference product is manufactured.
- The qualitative formulation of the reference product. (3.9%)
- Certificate of Analysis of the reference product. (8.5%)
- Shipment and storage details of the reference product to the sponsor. (8.8%)
- Copies of the immediate container label as well as the carton or outer container label of the reference product. (4.9%)
- The method of manufacture of the reference product is claimed by the applicant to be the same.
- Procurement information of the reference product:

  • Copy of licensing agreement/s if relevant
  • Distribution arrangements/agreement/s if relevant
  • Copy of purchase invoice (to reflect date and place of purchase) (4.9%) [5]

The above deficiencies were the largest observed in this category and were quantified as 31%.

The bioequivalence study aims to confirm the similarity of two formulations of the test and reference product. Formulation comparison is imperative, as there may be formulation effects, which alter the bioavailability of the test product, and therefore, qualitative comparison with the reference would need to be assessed. There was 42% of the deficiencies depicted in Table 4 requesting the confirmation of similarity between the formulation of the test and reference products as well as any changes which have been made to the biobatch if the submission received was older than five years. The data requirements are confirmation of the following to ensure no significant changes occurred: unit formulation, manufacturing procedure and equipment, site of manufacture of final product and manufacturer of the API, and overall product specifications. This is to ensure that there were no major amendments made to the product which may negatively impact on the quality of the product compared to the biobatch.

Comparison with RW1, RW2, and RW5 Applications (2020–2021)

Tables 2, 3, 4 and 5 also illustrate the similarities on the common deficiencies witnessed in applications finalised between 2011 and 2017 and those assessed between 2020 and 2021. The additional row indicating the frequency of deficiency in 202–2021 shows all the deficiencies that were

identified. This confirms that the standards of assessment have been maintained as the identified deficiencies comprised of more than 80% of the deficiencies already identified in the 2011–2017 sample. The distribution of deficiencies is also similar to that observed in Fig. 3 with dissolution as the highest category (23%) and sample analysis (24.2%) followed by inspections (13.4%). The deficiencies that were observed only in the 2020–2021 applications are largely on the request of Case reports forms and the Statistical Analysis Software (SAS) report for raw data as well as the executed BMR (batch manufacturing records) of the biobatch. These were previously not a requirement. The Case report forms were assessed during inspections as well as the executed BMRs and therefore not incorporated in the quality and bioequivalence assessments; however, these are now requirements by SAHPRA and relevant documents should be included in the dossiers.

Comparison of the Deficiencies with Those of Other Well-Known Regulatory Authorities

Only a few reports have been published on biostudy common deficiencies from other regulatory authorities. The USFDA reported on these in 2012 using Abbreviated New Drug Application (ANDA) applications received between 2001 and 2008 to identify the most commonly occurring biostudy deficiencies [14]. The two most common deficiencies related to dissolution are method and specifications which constitute 23.3% of the applications and bioanalytical method validation and/or report found in 16.5% of the applications [14] .

The USFDA noted that the establishment of an online dissolution method database has helped greatly in improving the quality of the ANDA submissions. Reducing the deficiencies to 15.5% in 2006–2008, thus accelerating the approval of generic products [14]. The observed deficiency on in vitro dissolution testing is comparable to the deficiency recorded as the highest in SAHPRA applications at 18%.

On bioanalytical method validation and/or report, the USFDA found the most frequent deficiencies include a lack of SOPs, no data showing long-term stability of API in frozen samples of biological fluid, and incomplete sets of bioanalytical raw data [14]. These are similar to those observed in Tables 3 and 5 for sample analysis and bioanalytical report issues witnessed by SAHPRA. Issues relating to the lack of inclusion of relevant SOPs in the bioanalytical report and the raw data of the bioanalytical report were observed as 23% by SAHPRA. The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The Bioanalytical methods used must have adequate sensitivity and accuracy, as well as selectivity that will make it possible to quantify the API in the presence of its metabolites or of endogenous compounds that may interfere with the determination of the compound in biological fluids [28]. The samples should be well characterised, fully validated, and documented to yield reliable results that can be satisfactorily interpreted [6]. This section, therefore, covers this aspect to ensure the appropriateness of the bioanalysis and reliability of the validated methods.

The other components reported by the USFDA were potency and formulation, unjustified exclusion of subjects, analytical issues, and long-term stability [14]. This confirms the similarity in the quality of evaluation of the submitted biostudies between SAHPRA and the USFDA.

WHO PQTm also conducted a study for applications submitted between April 2007 and December 2010 [15]. The deficiencies observed were categorised as follows: clinical study information, subject sample analysis, audit and monitoring information, statistical calculation, analytical method validation issues, and an unacceptable reference product [15]. The deficiencies were quantified according to the therapeutic category of the submission, for example, 15% of the dossiers on reproductive health (treatment category) included incorrect pharmacokinetic/statistical calculations that required revision and re-calculation. The deficiencies observed from the components mentioned were very similar to those reported in Tables 2, 3, 4 and 5 confirming the similarity of the quality of evaluations. The similarity is also witnessed in the work published by WHO PQTm in 2020 which stipulates an update on the qualitative common deficiencies in the biostudy reports submitted [32] .

Conclusion

The study included the collection of a list of common deficiencies on biostudies from applications finalised over a seven-year period and highlighted the most common deficiencies requested by SAHPRA. In addition, a recent study was conducted which confirms that the standards of assessments have been maintained as the deficiencies reported between 2011 and 2017 are similar to those observed in the 2020–2021 assessments. This, therefore, provides transparency to pharmaceutical companies on deficiencies to address before biostudy submissions are made to SAHPRA. The findings also show that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies such as the USFDA and WHO PQTm. These findings will guide pharmaceutical companies, manufacturers, and CROs in submitting quality biostudies in the future which will thereby allow accelerated access to medicine for patients. This in turn will reduce the turnaround product registration timelines for SAHPRA. Moreover, the deficiencies identified will assist assessors from the different countries to improve on their bioequivalence assessments.

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Author Contributions
LM developed the study design, collected and analysed the data, interpreted the results, and wrote the first draft of the manuscript. ML developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results, and reviewed the manuscript. JJ developed the study design, provided guidance on the data analysis, interpreted the results and relevance of the results, and reviewed the manuscript.

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Declarations

Conflict of interest
No conflicts of interest that are directly relevant to the content of this article.

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