Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-021-00359-9

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ORIGINAL RESEARCH

Common Deficiencies Found in the Active Pharmaceutical Ingredient (API) Section of Non-sterile Generic Products Submitted for Registration by SAHPRA

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Received: 13 July 2021 / Accepted: 17 November 2021

Abstract

Purpose This research study aims to determine the qualitative and quantitative common deficiencies included in the API section of dossiers submitted to SAHPRA. The study was conducted retrospectively over a 7-year period (2011–2017) for non-sterile generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. In this period, the restricted part of the CTD was evaluated when needed therefore this was not conducted on all applications. The requirement to evaluate the restricted part for all applications was initiated in January 2020, thus, a separate study has been conducted to identify the common deficiencies in the restricted part.

Methods There were 2089 applications finalised between 2011 and 2017 and in order to attain a representative sample for the study, the multi-stage statistical sampling called the 'stratified systematic sampling' was selected as the method of choice. Sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation with a 95% confidence level, resulting in the selection of 325 applications. Subsequently, all the deficiencies were collected and categorised according to CTD subsections. For the restricted part study, all new applications evaluated between January to May 2020 were used.

Results A total of 1130 deficiencies were collected from 325 applications sampled. The majority of the identified deficiencies were from Module 3.2.S.3.1 (19.38%) on characterisation, Module 3.2.S.1.3 (19.11%) on general properties, Module 3.2.S.4.1 (10.44%) on specifications and Module 3.2.S.4.3 (8.32%) on validation of analytical methods. The study on the restricted parts included the five most common deficiencies that SAHPRA has identified, which are similar to those observed from the 2011–2017 applications. This confirms that the quality of the evaluations has been maintained over the years. Comparison of the deficiencies with those reported by other agencies such as the USFDA, EMA, WHOPQTm and TFDA are discussed with similarities clearly outlined.

Conclusions The most common deficiencies observed by SAHPRA were extensively discussed. These findings could serve as a guidance for API manufacturers to submit better quality APIMFs which will improve turnaround times for registration and accelerate access to medicines for patients.

Keywords South African Health Products Regulatory Authority (SAHPRA) · Common deficiencies · Active pharmaceutical ingredient master file (APIMF) · Drug master file (DMF) · Common technical document (CTD) · Active pharmaceutical ingredient (API)

Introduction

The South African government established a medicines regulatory authority in 1965 shortly after the implementation of the Medicines and Related Substances Act (Act 101 of 1965). [1] The quality and efficacy aspects of finished pharmaceutical products (FPP) are evaluated by the Department, Pharmaceutical Evaluations and Management (PEM) pre-registration Unit within SAHPRA. The pre-registration

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Published online: 02 December 2021

Unit utilised 15–20 external experts as evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provided the necessary support to the Unit and the Committee meetings served as a quality assurance measure for all applications. Committee members provided technical and scientific advice for evaluations in the pre-registration Unit. This meant that each report on the assessment of the information provided in the dossier was discussed in the meeting before communication with the applicant. The applications are submitted in the form of a dossier in the common technical document (CTD) format to the Health Products Authorisation (HPA) and distributed to different Units within SAHPRA for evaluation. A CTD is an internationally agreed format for the preparation of new product applications for submission to regional regulatory authorities. The CTD format is divided into five modules as illustrated in Fig. 1 [2].

The quality part of the dossier is divided into two main sections namely, information on the active pharmaceutical ingredient (API) and information on the finished pharmaceutical product (FPP). A list of deficiencies referred to as recommendations are then produced from the evaluation process and communicated to the applicant. The applicants are given three months to respond and update the dossiers with the requested information necessary to verify the quality of the product. There were no specified rounds of communication given between the applicant and the agency. Once all the requirements have been met by all the Units and the quality of the drug product is considered safe and efficacious as required by the agency, the FPP is finalised and is recommended for registration.

SAHPRA receives the API part in the form of a DMF/APIMF (applicant part), or requirements supported by a Certificate of Suitability (CEP) or a Certificate of prequalification (CPQ). The CEP and CPQ are certificates allocated for APIs where DMFs have been approved by EDQM [3] and WHO-PQTm [4], respectively. Authorities such as EMA, [3] USFDA, [5] TDFA [6] and Health Canada [7, 8] have implemented the APIMF/DMF procedure. In this procedure, the complete data are assessed including confidential information from manufacturers. This procedure has not been adopted by many authorities due to insufficient resources and capacity, therefore, only the applicant part of the DMF is submitted and assessed. International medicines regulators worldwide such as TFDA [6], USFDA [9, 10] and EMA [11–15] as well as WHO-PQTm [16, 17] have published several articles on various regulatory aspects in order to promote transparency between the authority and the manufacturers. Those publications are intended to assist applicants to improve the quality of their submitted dossiers, in order to facilitate and accelerate the approval process. This study therefore aims to highlight the common deficiencies observed from the API section submitted by APIMF holders to the health authority, SAHPRA. It is aimed at guiding the manufacturers in submitting better quality APIMFs which will decrease turnaround times for registration and accelerate access to medicines for patients.

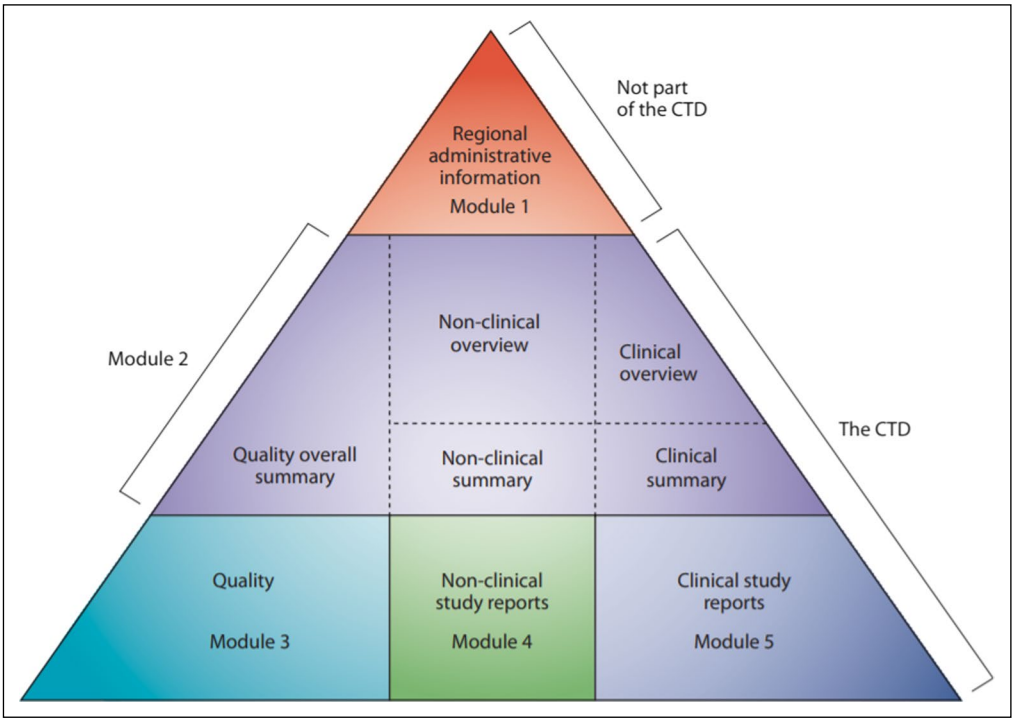

Fig. 1 The organisation of the CTD into five modules. Module 1 is intended to be region specific while the rest of the modules are common for all regions. [2]

Methods

Over the 7-year period (2011–2017), 2089 applications were finalised by SAHPRA. These applications were used to study the trends observed by the authority in order to refine the current processes and inform industry of the current requirements from a scientific viewpoint. Thus, due to the large number of applications received, a statistical sampling method became a requirement for this research. Sample selection in this study should provide a true representation of the population enabling the results to be generalised to the population as a whole. In statistics, stratified sampling is a method of sampling from a heterogeneous population which can be partitioned into subpopulations. [18] It involves dividing the entire population into homogeneous groups called strata. [18] The sampling method ensures that each subgroup is adequately represented within the whole sample of a research study. Sampling of medicinal products from a large population would require stratified sampling due to the different critical variables involved such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product. Thus, stratified sampling would be suitable for the population in this research study. In addition, systematic sampling is preferred as opposed to random sampling in order to ensure that proportional number of units are selected accordingly at the respective strata. [19–22] The multi-stage sampling technique used is therefore called stratified systematic sampling.

Sample size determination can be obtained using various methods such as a census for small populations, a sample of a similar study, published tables or statistical formulae. [23–25] For sample size calculation, the formula reported by Israel G. D, (1992) [24] contains three variables which are a requirement when determining a sample size (see Supplementary Information for equations and calculations). The variables are; level of precision, level of confidence and the degree of variability. [24, 25] The level of precision used is often expressed in percentage points and described as the percentage error which is selected as ± 5%. [24] In this regard, the level of confidence is therefore 95%. Cohran [22] developed an equation to yield a representative sample for proportions of large samples where the confidence level corresponds to a Z-score which is calculated as 1.96 for the selected confidence level as per the developed equation. The degree of variability (p) refers to the distribution of attributes in the population and a 50% variability is ideal for a heterogeneous population as it gives higher variability. [21, 22] thus a proportion of 50% (0.5) was selected. This equation was used in calculating the sample size for this research study. The calculated sample size obtained was 325 from a population of 2023. Comparison of the calculated sample size with the table reported by F.B. Mahammad [26] for a given population size showed a similar reported value for a population of 2000 of 322 with the same confidence interval and level of precision. There are many other tables reported [24–26] with sample size ranging between 322 and 333. The kth term serves as a constant value used for systematic sampling and is aimed at ensuring that adequate representative units are selected in each strata. This was calculated as six, which means selection was conducted at each 6th value in order to attain the representative sample size.

The full history of all products finalised between the 7-year period (2011–2017) were collected. The history comprises of all communication between the authority and applicants until finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses. These paper documents were obtained from the P&A Committee meeting minutes and the registry files where all documents relating to the product are kept. 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 multiple follow-up rounds of communication.

For the investigation of common deficiencies in restricted parts of the dossier, initial query letters sent between January and May 2020 were obtained and the recommendations recorded. The investigation is initiated in order to alert pharmaceutical companies of the common deficiencies identified by SAHPRA in the restricted parts, allowing them to submit dossiers with the required information from the onset. These were obtained from SAHPRA's electronic dossier folder and recorded.

Information for 2018 and 2019 is not included in this study due to the disruptions caused by the protesting action in 2018 and the move to the new premises in 2019 which halted production. During the transition of the authority from MCC to SAHPRA, SAHPRA staff continued to be housed in Civitas building in Pretoria with the NDoH employees. From April 2018, the department employees working in the Civitas building embarked on a protest action because of concerns about working conditions in the building. SAHPRA as a Sect. 3A public entity, moved into new premises at the end of 2018. Flow of submissions regained momentum by the middle of 2019.

Results

Stratified systematic sampling ensures that sampling is representative and not biased and that all critical variables are considered. Aspects such as the applicant, the dosage form,

the API used, the therapeutic category and finalisation time of the drug product were considered as important variables. Out of the above five mentioned variables, the most critical and of importance is the therapeutic category since we are dealing with pharmaceutical products.

Regulation 25 of Act 101 classifies and categorise medicines in South Africa as follows:

- Category A for Medicines which are intended for use in humans and are without manipulation, ready for administration;
- Category B for Medicines which cannot be administered without further manipulation; and
- Category C for Medicines intended for veterinary use, which are without further manipulation, ready for administration [27].

All medicines in the population are category A. This category is subdivided into 34 pharmacological classifications, some of which are subdivided further. Each therapeutic category is considered a stratum. These are grouped into 33 categories. The sample size in each stratum as illustrated in Table 1 varies according to the relative importance of the stratum in the population, i.e. percentage contribution. For example, if 16% of the population are antiviral agents, then 16% of the sample should contain products in that group.

The sample sizes of all strata were combined to attain a representative sample size of 349 products. The rounding down of the kth term resulted in slightly more samples being selected in comparison to the findings on statistical tables and calculated values with the acceptable range of 322–333 as indicated above. Therefore, 330 samples were selected, five of these were omitted from the study as they undertook a different registration process called the ZaZiBoNa collaborative assessment process which SAHPRA joined in June 2016 [28] Therefore, the samples used in the study were 325 as per calculations (see Supplementary Information for equations and calculations).

The deficiencies were collected and information populated in the respective Microsoft Excel® Worksheets and quantified using the complete history of finalised products. This research focuses on the API, 3.2.S part of the CTD. The 3.2.S part of the quality section of the CTD consists of sections stipulated in Table 2 regarding the API used in the product. It contains seven sections in which five have subsections.

A total of 1130 API deficiencies were collected from 325 letters from products that were finalised in 2011–2017. The deficiencies observed were all collected as indicated in Table 3. The table outlines all the deficiencies recorded from 325 letters in the API section. These were categorised per subsection and quantified. The quantities per subsection were recorded as the number of times they were observed in the recommendation letters, then as the percentage of a subsection in a CTD section and lastly as a percentage in the whole 3.2.S CTD section. Figure 2 summarises the results of the common deficiencies per subsection in percentages thereby showing the frequent deficiencies.

In 2020, SAHPRA updated the requirements and introduced the request of the restricted part of generic products. A study was conducted which seeks to provide common deficiencies observed from the restricted part. This was conducted on applications evaluated between January and May 2020 by the PEM pre-registration Unit (business-as-usual, BAU section). The deficiencies collected from the 20 initial letters are stipulated in Table 4. Overall, 275 deficiencies were observed from the letters communicated to applicants.

Discussion

Common Deficiencies Observed by SAHPRA in the Submitted DMF/APIMFs

Highest Common Deficiencies

Subsection 3.2.S.3.1 had the highest deficiencies of 19.38% in section 3.2.S. It is a requirement that proof of correctness of the structure be submitted if no official standard is available in which case sufficient evidence, such as Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR), Infrared (IR), Mass Spectroscopy (MS), elemental analysis, etc., (with interpretation) should be provided in support of the structure and stereochemistry. These were either not submitted (1.5%), submitted with no interpretation (34.1%) or legible copies (35.1%) were not submitted and were therefore requested. The other 6.0% of the deficiencies were due to the characterisation of the polymorphic form. In instances where the API exists in more than one polymorphic form, the applicant is required to submit data on consecutive batches confirming that during the manufacturing process only one form is consistently produced. Studies should be performed comparing other polymorphic forms found in literature to the required polymorphic form. This is normally done by comparing their powder X-ray diffraction- (pXRD), differential scanning calorimetry- (DSC) or Fourier transform infrared (FTIR) spectra. Polymorphism is when the same molecule crystallizes into more than one type of crystal. The polymorphs are made of the same atoms but in different crystalline arrangements. The solubility and hence the bioavailability may be very different in the two different arrangements. [29] One API could have different polymorphic forms which differ in internal solid-state structure and may, therefore, possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. [30, 31] The unexpected appearance

Table 1 The different strata (pharmacological classifications) generated with respective population and sample sizes

Pharmacological/therapeutic classifications	Population (N*)	%	Sample (n_*)
1.1 Central analeptics 1.2 Psychoanaleptics (antidepressants) 1.4 Respiratory stimulants	103	4.9	17
2.1 Anaesthetics 2.2 Sedatives, hypnotics 2.5 Anticonvulsants, including anti-epileptics	149	7.1	25
2.6 Tranquillisers 2.6.5 Miscellaneous structures	191	9.1	32
2.7 Antipyretics or antipyretic and anti-inflammatory analgesics 2.8 Analgesic combinations 2.9 Other analgesics 2.10 Centrally acting muscle relaxants and	51	2.4	9
3.1 Antirheumatics (anti-inflammatory agents) 3.2 Non-hormonal preparations 3.3 Anti-gout preparations	51	2.4	9
4.0 Local anaesthetics	5	0.2	1
5.2 Adrenolytics (sympatholytics) 5.3 Cholinomimetics (cholinergics)	69	3.3	11
5.4.1 Anti-Parkinsonism preparations	68	3.3	11
5.6 Histamine	10	0.5	2
5.7.1 Antihistaminics	29	1.4	5
7.1 Vasodilators, hypotensive medicines	51	2.4	9
7.1.3 Other hypotensives	328	15.7	55
7.1.5 Vasodilators—peripheral	48	2.3	8
7.3 Migraine preparations	25	1.2	4
7.4 Lipotropic agents 7.5 Serum-cholesterol reducers	92	4.4	15
8. Medicines acting on blood and haemopoietic system 8.2 Anticoagulants 8.4 Plasma expanders	13	0.6	2
10 Medicines acting on respiratory system 10.2 Bronchodilators 10.2.1 Inhalants	88	4.2	14
11. Medicines acting on gastro-intestinal tract 11.1 Digestants 11.4.3 Other 11.5 Laxatives 11.9.2 Special combinations and 11.10 Others	72	3.4	12
13.4.1 Corticosteroids with or without anti-infective agents 13.4.2 Emollients and protectives 13.9 Radiation protectants 13.11 Acne preparations 13.12 Others 14. Preparations for treatment of wounds 14.2 Wound dressings	15	0.7	3
5.8 Preparations for the common cold including nasal decongestants 16.1 Nasal decongestants 16.3 Surface anaesthetics 16.4 Naso-pharyngeal and bucco-pharyngeal antiseptics	24	1.1	4
18.1 Diuretics 18.2 Antidiuretics 18.3 Ion-exchange preparations 18.8 Ovulation controlling agents	24	1.1	4
20.1.1 Broad and medium spectrum antibiotics 20.1.2 Penicillins 20.1.6 Topical antibiotics	125	5.9	21
20.2 Antimicrobials, Other than antibiotics	13	0.6	2

Table 1 (continued)

Pharmacological/therapeutic classifications	Population (*N**)	%	Sample (n_*)
20.2.2 Fungicides 20.2.3 Tuberculostatics 20.2.6 Medicines against protozoa	34	1.6	5
20.2.8 Antiviral agents	213	10.2	36
21.1 Insulin preparations 21.2 Oral hypoglycaemics	37	1.8	6
21.3 Thyroid preparations	12	0.6	2
21.5.1 Corticosteroids and analogues	8	0.4	1
21.8.2 Progesterones with or without oestrogens	10	0.5	2
21.12 Hormone inhibitors	43	2.1	7
26 Cytostatic agents	31	1.5	5
32 Other substances or agents	10	0.5	2
34 Others	47	2.2	8
TOTAL	2089	100	349

Table 2 The CTD sections and subsections for Module 3.2.S regarding the API

CTD sections and subsections	Content
3.2.S.1	**General information**
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General properties
3.2.S.2	**Manufacture**
3.2.S.2.1	Manufacturer
3.2.S.2.2	Description of manufacturing process and process control
3.2.S.2.3	Control of Materials (Restricted part)
3.2.S.2.4	Control of critical steps and intermediates (Restricted part)
3.2.S.2.5	Process Validation and/or Evaluation (Restricted part)
3.2.S.2.6	Manufacturing process development (Restricted part)
3.2.S.3	**Characterisation**
3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	**Control of active pharmaceutical ingredient**
3.2.S.4.1	Specifications
3.2.S.4.2	Analytical procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of specifications
3.2.S.5	**Reference standard or materials**
3.2.S.6	**Container closure system**
3.2.S.7	**Stability**
3.2.S.7.1	Stability summary and conclusions
3.2.S.7.2	Post approval stability protocol and stability commitment
3.2.S.7.3	Stability Data

or disappearance of a polymorphic form may lead to serious pharmaceutical consequences therefore; control is crucial.

A classic example which showcases the importance of polymorphism is ritonavir which was originally dispensed as an ordinary capsule, with a polymorphic form of form I. [32] During development in 1996, only the polymorph now called form I was found, but in 1998, a lower free energy, more stable polymorph (form II) appeared. [32] This more stable and less soluble crystal form compromised the oral bioavailability of the drug. This led to the removal of the oral capsule formulation from the market.

Table 3 List of API common deficiencies recommended by SAHPRA in the products finalised by the pre-registration unit between 2011and 2017

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.1	The documentation must comply with the SA Guide to GMP Chapter 4, Requirements for Documentation, including at least a unique identification, version and date. In addition, a declaration that it is current must be included	55	17.57	4.9
3.2.S.1 (3.2.R.4)*	Include a comparison of the method of synthesis, specifications and batch analysis data to confirm similarity or outline differences between the different API manufacturers	18	5.75	1.6
3.2.S.1 (3.2.R.3)*	Submit an updated CEP as observed from the EDQM website or ensure that the declaration of access to give the applicant access is signed by the CEP holder	24	7.67	2.1
3.2.S.1.3	State the polymorphic form of the API used	14	4.47	1.2
3.2.S.1.3	Provide evidence of occurrence of isomers and chirality where applicable. The absence should also be confirmed	11	3.51	1.0
3.2.S.1.3	The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The investigation should include water and the solvent(s) relevant to the product formulation	157	50.16	14
3.2.S.1.3	Include information on the hygroscopicity of the API under physical properties	26	8.31	2.3
3.2.S.1.3	The physical and chemical properties of the API, including e.g. solubility, particle size, hygroscopicity should be included when a CEP has been submitted	8	2.56	0.7
		313		
3.2.S.2.1	The name, business and physical address of each manufacturer of the API being applied for (including any intermediate manufacturer) should be stated	3	3.1	0.3
3.2.S.2.2	A short description of the synthesis and a flow chart which includes the structures and stereochemistry of starting materials and intermediates; reagents, catalysts, solvents, isolation and purification; and any other relevant aspects were not included. This should be submitted	58	59.2	5.1
3.2.S.2.2/3	The starting material proposed is considered complex. Include the tests and specifications as well as the method of synthesis of the starting material or a Certificate of analysis (CoA) to confirm that the starting material is adequately controlled	13	13.3	1.2
3.2.S.2.3	Include the complete name and address of the manufacturer of the starting materials	10	10.2	0.9
3.2.S.2.3	Provide information with respect to control of critical steps and intermediates in the manufacturing process description	7	7.2	0.6
3.2.S.2.3	Briefly describe if there were recovery of materials or solvents (if any) in the method of synthesis and how they were conducted	3	3.1	0.3
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates used in the manufacturing process of the API	4	4.1	0.4
		98		
3.2.S.3.1	Provide interpretation of spectra, graphs and figures regarding the elucidation of the structure of the API	94	35.1	8.3
3.2.S.3.1	Legible spectra, graphs and figures regarding the elucidation of the structure should be submitted	99	34.0	8.8
3.2.S.3.1	Provide proof of correctness of structure. Spectra, graphs and figures were not submitted to support the correctness of structure	4	1.5	0.4
3.2.S.3.1	Two polymorphic forms have been reported. It should be demonstrated that the one polymorphic form remains unchanged during storage. This is regardless of the fact that the synthetic route yields only one form. State if the identity test can discriminate between the different polymorphs	17	6.3	1.5

Table 3 (continued)

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.3.2	Provide a description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities	17	6.3	1.5
3.2.S.3.2	Provide a description of possible degradation products	32	11.9	2.8
3.2.S.3.1	In the case of enantiomers an additional test is required to confirm the identity of the enantiomer and should be controlled in the final API specifications	5	1.9	0.4
		268		
3.2.S.4.1	Include particle size during stability for micronised API to ensure that the API has a well-defined dissolution behaviour	16	6.9	1.4
3.2.S.4.1	Tighten the specifications for individual impurities and total impurities in accordance to ICH guidelines and submitted batch analysis data	10	4.3	0.9
3.2.S.4.1	Include a genotoxic impurity in the final API specifications or provide a justification for its omission	2	0.9	0.2
3.2.S.4.1	The API specifications must be expanded to include a limit for residual solvents including benzene and the relevant validated control procedure must be described	18	7.7	1.6
3.2.S.4.1	Include a specification for the test for polymorphism to ensure that the correct polymorph is consistently formed	10	4.3	0.9
3.2.S.4.1	Include a test for microbial purity/content	6	2.6	0.5
3.2.S.4.1	Include enantiomeric purity in the final specifications to ensure that the enantiomer is consistently controlled	23	9.9	2.0
3.2.S.4.1	Tighten the assay release and stability specification to 95—105% in accordance with the SAHPRA guidelines and include this as a percentage label claim or in mg	7	3.0	0.6
3.2.S.4.1	Include signed and dated specifications by authorised personnel and confirm that they are the same as the FPP's API specifications	9	3.9	0.8
3.2.S.4.1	Bring the API specifications in line with those indicated in a recognised pharmacopoeial monograph and if a CEP is submitted the specifications must be in line with the European Pharmacopoeial monograph	12	5.2	1.1
3.2.S.4.1	Include the specifications for particle size in the FPP manufacturer's API specifications, if applicable	5	2.1	0.4
3.2.S.4.3	Provide details of the reference standards used for validation of related substances	3	1.3	0.3
3.2.S.4.3	Submit validation data for the assay method of the API, residual solvents and related substances including the respective supporting chromatograms	32	13.8	2.8
3.2.S.4.3	The FPP manufacturer must include partial validation or verification for APIs that are pharmacopoeial	13	5.6	1.2
3.2.S.4.3	Include a more stability indicating method than Thin Layer Chromatography (TLC) as the pharmacopoeia includes the use of one, such as High-Performance Liquid Chromatography (HPLC)	5	2.1	0.4
3.2.S.4.3	Indicate the stability of the reference standard solution and the sample solutions	5	2.1	0.4
3.2.S.4.3	Inconsistencies observed in the validation data submitted and clarification required	36	15.6	3.2
3.2.S.4.4	Provide numeric values for the data, "complies should be avoided"	5	2.1	0.4
3.2.S.4.5	Provide justification of the limits set for final API specifications	8	3.5	0.7
3.2.S.4.5	Provide supporting data to prove the justification of the exclusion of certain residual solvents from final specification testing with results tested on six consecutive batches	8	3.5	0.7
		233		

Table 3 (continued)

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.5	Provide comparative overlaid IR spectra of the in-house reference standard with the pharmacopoeial reference standard/ qualification of the working standard with the reference standard	26	42.0	2.3
3.2.S.5	Provide the purification method for the in-house reference standard	3	4.8	0.3
3.2.S.5	Provide the CoA of the pharmacopoeial reference standard and/or the in-house reference standard as well as the source of the reference standard	33	53.2	2.9
		62		
3.2.S.6	Provide a description of the container closure system(s) used	52	76.5	4.6
3.2.S.6	Identity of materials of construction of each primary packaging material as well as the identification test used	10	12.3	0.9
3.2.S.6	Submit control procedures, specifications and CoAs of the primary packaging material	9	11.1	0.8
		71		
3.2.S.7.3	Provide additional stability data for the consideration of the requested retest period	42	56.0	3.7
3.2.S.7.3	The out of specification results and justification provided are not accepted and therefore the requested re-test period not granted	2	2.7	0.2
3.2.S.7.3	Indicate the type of batch e.g. pilot/production/experimental as well as the batch size used	12	16.0	1.1
3.2.S.7	Include full stability data for a consideration of the retest of an API. This section should be submitted in compliance with the SAHPRA guidelines	29	25.3	2.6
		85		

(3.2.R.3)* This is a section relating to 3.2.S but has been placed under the regional Sect. 3.2.R.3 on the submission of a CEP

(3.2.R.4)* This a section relating to 3.2.S in cases where more than one API source has been applied for, this is placed under the regional Sect. 3.2.R.4 on multiple API manufacturers

Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.1 elucidation of structure, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.2 analytical procedures 3.2.S.4.3 validation of analytical procedures, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

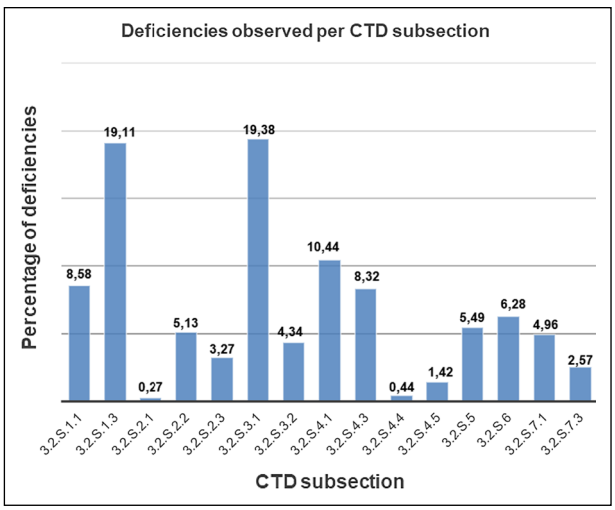

Fig. 2 Distribution of deficiencies per API CTD subsection

Second Highest Common Deficiencies

Figure 2 shows that subsection 3.2.S.1.3 had the second highest number of deficiencies. The recommendations were based on physico-chemical properties of the API. Aspects such as polymorphism, chirality, isomerism, solubility and hygroscopicity of the API were not addressed by the API manufacturer and were therefore requested. Close to 50% of these recommendations were requesting the solubility of the API at physiological pH (1.2–6.8) with several buffered solutions and with solvents relevant to the product formulation and the temperature at which the solubility studies were conducted, to be included. This is critical information that assist in determining the Biopharmaceutics Classification System (BCS) class of the API and hence establish its behaviour during dissolution and bioequivalence studies. Solubility is critical to determine the formulation, the process and the performance of a product, therefore a study is normally required to investigate the solubility of each API. Hygroscopicity on

Table 4 The common deficiencies observed from 20 initial query letters from 31 APIMFs in the restricted part

Subsection	Deficiency	Quantity	% subsection	Request rate (%)
3.2.S.2.3	The API starting materials proposed are complex and form a large part of the backbone of the final API, therefore these require to be well characterised and adequately controlled during the synthesis of this starting material. This therefore requires further redefinition of the starting materials in accordance to the ICH Q7 and ICH Q11 guidelines. In addition, submit the specifications of the starting material to confirm that it is adequately controlled	31	11.3	100
3.2.S.2.3	State the scale of manufacture, the typical batch size, and the maximum batch size (the range) for which the process is described as well as quantities (mass or molar equivalents) of the starting materials and yield ranges for each step of the synthesis	31	11.3	100
3.2.S.2.3	Confirm that no alternative processes are applied during the proposed manufacturing process	30	10.9	96.8
3.2.S.2.3	State if reprocessing or reworking of the API or reaction intermediate occurs. If so, describe this in detail	30	10.9	96.8
3.2.S.2.3	Briefly describe the recovery of materials or solvents (if any), including how the materials or solvents are recovered	31	11.3	100
3.2.S.2.3	Where particle size is considered a critical attribute of the API, the milling/micronisation equipment, process parameters and procedures should be described	23	8.4	74.2
3.2.S.2.3	Provide equipment used during each step of the manufacturing process and operating conditions (e.g. temperature, pressure, pH, time)	27	9.8	87.1
3.2.S.2.3	Confirm that no blending of the final batches is allowed. Should allowance be made for blending then clearly indicate which criteria/tests is/are used to ensure that the individual batch incorporated into the blend meet specifications set for the final product prior to blending	21	7.6	67.8
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates, including the reaction conditions, completion of individual reaction steps and the identity and purity of the isolated intermediates	25	9.1	80.6
3.2.S.2.6	Indicate any significant changes made throughout the various development stages: these can be changes to the manufacturing process and/ or site of the API since production of earliest batches including non-clinical, clinical batches (e.g. bio-batch supplied to the FPP manufacturer) in comparison to scaled-up pilot and production batches (if applicable)	16	5.8	51.6
	Other	10	3.6	32.2
		275	**100**	

the other hand with 3.0% of the deficiencies will provide insight into the stability of the API and establish whether the API or formulation may be sensitive to moisture. Chirality and stereochemistry (1.7%) of the API are important aspects to be detailed in the structure of the API since other isomers are required to be controlled in the final API specifications if not in the intermediate specifications. The product can have several isomers which may be harmful to the patient even though the structures are similar, therefore isomers serve as impurities and should be controlled as such.

Third Highest Common Deficiencies

The third largest number of deficiencies in the subsections were from tightening specifications in view of the results submitted from batch analysis and stability data of the API. Sixty percent of the responses from applicants stated that the results were within the ICH guideline limites (ICH Q3A (R2)) [33] which was correct, while in other instances the applicant's limits would exceed the ICH limits and they would not provide a sufficient justification for this. ICH Q3A has the following impurity thresholds: identification

threshold (IT), reporting threshold (RT) and qualification threshold (QT). Impurities present that are higher than the IT needs to be identified and impurities higher than QT needs to be qualified for safety. The P&A Committee accepted this justification for reporting, identification and qualification thresholds as SAHPRA is an ICH observer. The second deficiency (1.6%) which led to the back-and-forth communication was applicants who would omit the test of a specific residual solvent, especially benzene which is a class I solvent, without providing supporting data of consecutive production batches to confirm that the solvent is not present in the final API and results being less than 30% of the ICH limit of 2 ppm. The presence of the following solvents in the manufacturing process result in this query being requested since they are known to be potential carriers of benzene; cetone, Toluene, Xylene, Hexanes and Isopropyl alcohol. Depending on where these are used in the manufacturing process, applicants are requested to control benzene in the final API or in the specific solvent specifications.

Fourth Highest Common Deficiencies

The fourth highest deficiencies were from subsection 3.2.S.1. The general information referred to here, is regarding the DMF/APIMF number if a DMF/APIMF is submitted, the CEP validity, if a CEP is submitted and comparison of manufacturing methods if more than one DMF is submitted. These are deficiencies which relate to the API section but do not have a specific location in the CTD and have been placed under regional information but will be discussed in this subsection. The DMF documentation must comply with the SA Guide to GMP Chapter 4 Requirements [34] for Documentation including at least unique identification, version and date. A declaration that it is current should be included. There was 17% of the deficiencies in the subsection relating to the DMF not being submitted as per the above requirements. This is crucial since different FPP manufacturers would source the same API manufacturer who would continually update the DMF/APIMF, therefore it is important for the authority to be informed of the latest version in order to generate a database and avoid duplication of evaluation in cases where the same API source is used by different FPP manufacturers. Also, DMF/APIMFs can be sent to multiple authorities resulting in frequent updates.

Information about the CEP is placed in the regional information Sect. 3.2.R.3 but will be discussed in this section since it relates to the API. Applicants are requested to submit the latest version of the CEP (2.4% of the 3.2.S section). The EDQM generally updates the status of each CEP therefore it is easy to find out if the submitted CEP is valid or not through the Certificate of Suitability database [3].

The section on multiple API manufacturers is also placed under regional information in Sect. 3.2.R.4. In cases where more than one API source is used it is required that the applicant provides a comparison of the method of synthesis, specifications and batch analysis to confirm similarity or outline differences between the API manufacturers which should be conducted by an independent laboratory. Although this may be obtained in the individual DMFs the summary provided assists in the evaluation and makes it easy for the evaluator to notice discrepancies, if any. Only 5.8% of the deficiencies in the subsection were as a result of this.

Fifth Highest Common Deficiencies

The fifth highest CTD deficiency subsection is 3.2.S.4.3. Almost 14% of the deficiencies in the section were due to applicants not submitting the required validation data of the analytical procedures used in specification tests. Other deficiencies were of discrepancies witnessed in the submitted validation data (15.6%) and partial validation data which should be submitted by the FPP manufacturer if they are using the same analytical procedures as the API manufacturer (5.6%).

Sixth Highest Common Deficiencies

Stability deficiencies (Modules 3.2.S.7.1 & 3.2.S.7.3) were the sixth most frequent deficiencies. In most cases, the deficiency was due to inadequate stability data being submitted for the consideration of a full retest period (56% of the requests in the subsection). Another common deficiency in this section was applicants submitting data which shows results that are out of specification with no valid justification for the results, these were only 2.7% of the subsection. For this reason, the retest period would not be allocated and a justification is requested. From the responses it was confirmed that the justifications provided differed per application, some stated that it was due to inaccurate results, others used stability results to insist on a widened specification limit, these were treated on a case-by-case basis depending on the specification. This also led to back-and-forth communication between the agency and applicants resulting in delayed finalisation.

Deficiencies from the Restricted Part

A comparison of the 2020 results was made with those reported on products finalised between 2011 and 2017. Table 3, subsection 3.2.S.2.2–3.2.S.2.4 shows similarity of the common deficiencies with those obtained in Table 4. For example, on the aspect of the complex starting material being submitted in Module 3.2.S.2.3, either the complete method of synthesis of starting material to simpler molecules as well as specifications or the CoA to confirm adequate control of the impurities was requested. This request is similar to that

reported in Table 4 for the redefinition of starting material amongst others. Another similarity amongst others was regarding the confirmation and description of residual solvent recovery. This investigation confirms that the quality of the evaluations has been maintained since critical aspects from the restricted part have always been requested by SAHPRA.

Comparison of API Common Deficiencies with that of Other Authorities

Comparison of API Deficiencies, SAHPRA Versus USFDA

The USFDA reported on how effective the DMF procedure is since it aims to avoid duplication of assessments by the authority. [10, 35] A DMF database was created and updated annually once all the requirements have been addressed. [10, 35] The authority does not quantify the deficiencies per subsection in the reports that have been made thus far.

The first deficiencies outlined under general information by FDA were aspects such as solubility, stereochemistry, hygroscopicity and polymorphism. These were also observed from the deficiencies received in SAHPRA applications which were the most frequent (19.1%) and discussed in detail above. The USFDA also included API characterisation as one of the common deficiencies observed with the applicant not submitting legible copies and analysis to confirm the polymorphic form. These are similar to the frequent recommendations sent to applicants by SAHPRA, making the Sect. 3.2.S.3.1, the highest of common deficiencies.

Another critical deficiency discussed by the USFDA which was the third highest for SAHPRA was the control of impurities (3.2.S.4.1). As discussed in the above section, all impurities in an API which are present at greater than the identification threshold (IT) as described in the ICH Q3A guidance need to be identified, in addition, impurities at levels greater than the qualification threshold (QT) need to be qualified for safety. [33] Thus, setting limits for unknown impurities higher than the IT will invariably lead to a deficiency. Similarly, not providing qualification information for the known impurities set higher than the QT will also not be acceptable. These were the frequent deficiencies observed regarding the individual impurities. This was followed by the request to tighten the total impurities' specifications based on the submitted stability results. Table 5 provides a comparison of the top five deficiencies from all the agencies.

Table 5 Comparison of the top five common deficiencies from the six regulatory bodies listed below

	USFDA	WHOPQTm	EDQM	TFDA	SAHPRA
1	3.2.S.1	3.2.S.2.3	3.2.S.2.3	3.2.S.2.2	3.2.S.3.1
2	3.2.S.2	3.2.S.2.2	3.2.S.3.2	3.2.S.2.3	3.2.S.1. & 3
3	3.2.S.3	3.2.S.7	3.2.S.2.2	3.2.S.4.1	3.2.S.4.1&3
4	3.2.S.4	3.2.S.3.2	3.2.S.2.4	3.2.S.4.3	3.2.S.7.1 & 3
5	3.2.S.5	3.2.S.4.1 & 5	3.2.S.4.4	3.2.S.7	3.2.S.2.2

Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

Comparison of API Deficiencies, SAHPRA Versus EDQM

The reported results on the top 10 deficiencies of new applications submitted to the EDQM are not quantitative and does not provide a thorough comparison. The EDQM reported the deficiencies annually from 2007 to 2016. [11–14] The top five deficiencies are modules; 3.2.S.2.3, redefinition of the starting materials required, 3.2.S.3.2, absence of the discussion of potential mutagenic and genotoxic impurities, 3.2.S.2.3, absence of discussion on the carry-over of impurities and by products from key materials in the process, 3.2.S.2.2, lack of details and poor description of the manufacturing process of the starting materials and 3.2.S.2.3 inadequate or poorly justified specifications to control the quality of starting materials. [11–14] From the above, it is witnessed that most deficiencies are from Module 3.2.S.2 and 3.2.S.3. This information is found in the restricted part of the dossier and SAHPRA only required the information when needed due to the sensitivity of information. Hence, the limited amount of API deficiencies for that section. It was recorded that 98 of the deficiencies (8.2% of the total deficiencies) were from the 3.2.S.2 section with 59% of them due to an insufficient flow diagram detailing the required information and 24% due to the redefinition of the starting materials and request of their specifications. With the introduction of the APIMF procedure, the study on the restricted part queries show that the redefinition of the starting material and other critical aspects of the restricted part are now requested for all applications by SAHPRA.

Comparison of API Deficiencies, SAHPRA Versus WHO-PQTm

WHO-PQTm reported on the common deficiencies witnessed from the 159 products assessed in the period January 2007–December 2012. [17] The qualitative and quantitative information provided allows for comparison of the deficiencies to those observed by SAHPRA. The most frequent subsection was found to be module 3.2.S.2.3 with 69.5% of deficiencies in the 3.2.S.2 section. This is a large difference to SAHPRAs 8.2% observed in the same subsection. The deficiencies included insufficient information provided on the starting material such as the manufacturer of the starting material, specifications of the starting material were either not provided or were unsatisfactory and the request for redefinition of the starting material. [17] API manufacturers have found it cheaper to buy intermediates instead of manufacturing them, hence the frequency of the deficiencies. Redefinition of the starting material is thus not provided or if provided, does not comply with the definition of ICH Q7 [36] and Q11 [37], which makes it difficult for regulatory authorities to assess potential impurities that may arise during preparation. [17] SAHPRA proposed the request of specifications and the CoA of the complex starting material instead of the redefined synthesis method. This gives assurance that the impurities are controlled and removed.

Comparison of API Deficiencies, SAHPRA Versus TFDA

A total of 471 DMF applications were filed between October 2009 and December 2011 by the TFDA and evaluated for common deficiencies. [6] The primary deficiencies observed in the initial assessments were in categories of the manufacturing process (31%) these were data for critical parameters, in-process controls and intermediates being incomplete. These were followed by API specification deficiencies (17%) where proposed limits were not in line with the pharmacopeia, then starting material deficiencies (16%), as redefinition of the starting material does not comply with the definition of ICH Q7 and Q11. [6] Lastly, analytical method validation (11%) where process validation was not included for the purification and sterilisation steps and validation was not conducted on consecutive batches. [6] It was clear that the analysis from the study may assist manufacturers in improving their submission quality and facilitates granting of DMF certificates. The difference and similarity of these with that reported by SAHPRA are highlighted in Table 5.

Conclusion

The study includes a list of common deficiencies observed over a seven-year period and highlighted the top six most common deficiencies identified by SAHPRA. In addition, with the implementation of the APIMF procedure in 2020, the common deficiencies requested from the restricted part were also highlighted. A list of all deficiencies observed was outlined. This study therefore provides transparency to pharmaceutical companies on deficiencies pertaining to Module 3.2.S. to address before dossier submissions are made to SAHPRA, this in turn will reduce turnaround timelines for product registration. Comparisons with other regulatory authorities showed that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies. These findings will guide the API manufacturers and pharmaceutical companies in submitting quality DMFs/APIMFs in future, which will thereby accelerate access to medicine for patients.

Acknowledgements
The P&A expert advisory Committee members who served between 2011 and 2017 and P&A pre-registration Unit staff are greatly acknowledged for their tireless efforts and expert guidance in ensuring that patients receive quality medicines in South Africa.

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, interpretation and relevance of the results and reviewed the manuscript.

Funding
The South African National Department of Health and SAHPRA assisted with the funding of the study.

Declarations

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

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s43441-021-00359-9.

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