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Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme

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Abstract

This study was undertaken to determine the type and extent of deficiencies in generic product dossiers in the therapeutic areas of HIV/AIDS, tuberculosis, malaria and reproductive health, as submitted to the WHO Prequalification of Medicines Programme. There were considerably more quality-related deficiencies in tuberculosis, malaria and reproductive health dossiers compared to HIV dossiers, especially in the category specification of active pharmaceutical ingredients, development pharmaceutics, manufacturing method and finished pharmaceutical product specifications. The deficiencies related to the efficacy/safety portion of the dossiers displayed a trend similar to that observed in the quality portion in that the most critical deficiencies such as an incorrect study design, the use of an unacceptable comparator or the failure to include a study occurred considerably more frequently in the tuberculosis, malaria and reproductive health dossiers than in the HIV dossiers. The frequency of dossier-related deficiencies as determined on screening and assessment of the dossiers seemed to be inversely related to the number of product dossiers that had been prequalified by the end of 2010. The results of this study stress the need for continued capacity building of local generic manufacturers, further development of pharmacopoeial monographs by WHO (PhInt) and other pharmacopoeial commissions, not least to promote development of generic products, as well as development of new guidelines (WHO guidelines for development of generic and paediatric products and a technology transfer guidance document are currently being finalized). To our knowledge, this is the first comprehensive review of the quality and efficacy/safety portions of generic product dossiers, originating from pharmaceutical companies in emerging markets, and comparison of dossier deficiencies across four critically important therapeutic areas.

Keywords

Prequalification, dossier deficiencies, generic medicines, quality, bioequivalence, HIV/AIDS, tuberculosis, malaria, reproductive health

Introduction

The World Health Organization (WHO) Prequalification of Medicines Programme started in 2001 in response to the absence of harmonized drug regulatory requirements across developing countries.[1] The task of the programme is to assure that medicinal products – mostly generic (multisource) products – supplied for procurement by United Nations Organization, governments, etc. meet WHO norms and standards with respect to quality, efficacy and safety (refer PQP website). Today, the scope of the programme has expanded from HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome) products to also cover medicinal products

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to treat tuberculosis (TB), malaria (MA), influenza and some neglected tropical diseases as well as reproductive health (RH) products and zinc products for diarrhoea (refer PQP website). Generic medicines play an important role in public health as they are well known to the medical community and are usually more affordable due to competition. The quality and efficacy/safety of a generic medicine must conform to the same standards as required of the originator's (comparator) products. Specifically, the generic product should be therapeutically and pharmaceutically equivalent to and thus, interchangeable with, the comparator product.[2] Therapeutic equivalence is usually demonstrated by testing the bioequivalence (BE) between a product and a suitable comparator product in a well-standardized pharmacokinetic study with a limited number of usually healthy subjects, thus obviating the need for clinical trials involving many patients to prove safety and efficacy.[2]

Inspection of manufacturing plants and laboratory quality control analysis only do not guarantee product quality and safety.[1] All processes involved in the manufacture of the active pharmaceutical ingredients (APIs) and the finished dosage forms need to be controlled.[1] Therefore, to ensure that the manufacturer has built quality into the product from the beginning, assessment of the product dossier prior to its acceptance is paramount.[1]

The assessment of product dossiers also provides manufacturers possessing limited experience interacting with stringent national regulatory authorities with an opportunity to understand the requirements and processes involved in such a process, since the expectations and requirements for prequalification are similar to the requirements of stringent national regulatory authorities. As the assessment and acceptance of a product dossier are necessary for the prequalification of a product, the time required to prequalify a product following application for prequalification will depend heavily on the content and organization of the product dossier. The higher the quality of a product dossier, the more quickly and efficiently the product can be assessed and prequalified. Dossiers possessing a large number of deficiencies will necessitate more interaction between the programme and the manufacturer during the assessment process, thus increasing the time to prequalification.

This study was undertaken to determine the type and extent of deficiencies in generic product dossiers in the therapeutic areas of HIV/AIDS, TB, MA and RH, as submitted to the WHO Prequalification of Medicines Programme. Deficiencies in both of the two main portions of a product dossier, quality and efficacy/safety, were examined. Further, a comparison of deficiencies in the dossiers submitted in the different therapeutic areas was made.

To our knowledge, this is the first comprehensive review of the quality and efficacy/safety portions of generic product dossiers, originating from pharmaceutical companies in emerging markets, and comparison of dossier deficiencies across four critically important therapeutic areas. Similar studies by US Food and Drug Administration (USFDA) and European Medicines Agency (EMA) investigated quality and/or efficacy/safety deficiencies in Abbreviated New Drug Applications (ANDAs) or new drug applications, but did not indicate the therapeutic areas studied, nor the origin of the dossiers.[3–9]

Materials and methods

This retrospective study encompassed all generic product dossiers in the therapeutic areas of HIV, TB, MA and RH received by the WHO Prequalification of Medicines Programme between April 2007 and December 2010. April 2007 was chosen as start of the study since a formalized screening procedure of dossiers submitted to the programme was initiated at that time.

Screening

Reports of screening of the submitted dossiers were reviewed for deficiencies identified. Submitted dossiers were screened with respect to completeness of the information on the quality and efficacy/safety of the product, including completed WHO quality and efficacy/safety summary forms (the latter forming the basis for the subsequent assessment reports generated by the assessors). Minimum expectations at the time of screening were: availability of process and analytical validation data, at least 6 months accelerated and 6 months long-term stability data for three batches of at least pilot scale and BE data or data justifying a biowaiver.

Assessment

Reports generated following the first round of assessment of the quality and efficacy/safety parts (typically BE study data in the latter case) of dossiers that had passed screening were reviewed for data deficiencies identified during the assessment. Specifically, issues that were forwarded to the applicant following an assessment, and hence affecting the final acceptance of the finished pharmaceutical product (FPP) quality and efficacy/safety parts of the dossier, were recorded. Deficiencies related to the FPP quality part were grouped into 10 categories (API specification,

development pharmaceutics, manufacturing process and controls, process validation, excipients, finished product specification, analytical methods and validation, container closure system, stability data and product labelling). These categories were chosen since they represent the FPP quality sections of a standard dossier. The efficacy-related deficiencies were similarly categorized into four main categories (study design/administration, clinical portion of the study, bioanalytical portion of the study and the statistical/pharmacokinetic analysis portion of the study). Deficiencies in the information available regarding the auditing and monitoring of the overall study were also tracked.

The results for the efficacy/safety portion are summarized and presented as the percentage of the total number of dossiers surveyed that contained each identified deficiency. The results for the quality part are presented as average number of deficiencies per dossier since all the reviewed dossiers had deficiencies in all the 10 quality categories.

API information can be provided to PQP as a certificate of suitability issued by The European Directorate for the Quality of Medicines, as an active pharmaceutical ingredient master file (APIMF), within the framework of the FPP dossier itself or recently through the use of a prequalified API.[10] Further, in some cases, the API-related data had already been assessed by PQP and considered acceptable in relation to a previously prequalified dossier. Depending on the option in each case, the extent of the API assessment by PQP will vary. For this reason, this review covered only deficiencies related to physico-chemical characterization and specification of APIs as used by the FPP applicant, since these two areas were common to all dossiers.

Further, common questions such as requests for justifications of proposed specifications, updated stability data and comments on preferred conditions for long-term stability studies (in most cases 30°C/75% relative humidity) were not included in the analysis, as such comments were sent out for nearly all the reviewed dossiers.

The status, as at the end of 2010, of dossiers accepted for assessment are tabulated by therapeutic area, in terms of number of dossiers prequalified, still under assessment or cancelled/withdrawn.

Results

Screening

Between April 2007 and December 2010, a total of 245 generic product dossiers were received and screened by the WHO Prequalification of Medicines Programme. Approximately 80% of HIV, 85% of TB, 35% of MA and 30% of RH dossiers received were submitted by manufacturers in India. Manufacturers in China and Indonesia accounted for 25% of MA and 33% of RH dossiers, respectively. The remaining dossiers were submitted by generic product manufacturers located in Argentina, Belgium, Brazil, Chile, Cyprus, Egypt, Eritrea, Ghana, Iran, Jordan, Kenya, Nigeria, Pakistan, the Philippines, Russia, Senegal, South Africa, Switzerland, Thailand, Vietnam and Zimbabwe.

The outcome of the screening of the dossiers is summarized in Table 1 and deficiencies observed during screening are shown in Figure 1.

Assessment

Of the 245 generic dossiers received and screened, a total of 178 dossiers were accepted for assessment (85 HIV, 48 TB, 25 MA and 20 RH dossiers). A total of seven dossiers were cancelled/withdrawn before

Table 1. Number of generic product dossiers received, screened and accepted for assessment between April 2007 and December 2010

	2007				2008				2009				2010			
	HIV	TB	MA	RH	HIV	TB	MA	RH	HIV	TB	MA	RH	HIV	TB	MA	RH
Dossiers received	15	15	7	16	46	17	16	5	31	18	12	3	20	15	6	3
Dossiers accepted during initial screening	3	0	1	6	19	8	1	1	9	10	5	0	9	5	5	2
Dossiers accepted after at least one round of WHO queries	8	12	2	4	24	5	8	3	8	5	3	3	5	3	0	1
Pending dossiers	0	0	0	0	0	0	0	0	10	0	1	0	6	4	1	0
Rejected dossiers	4	3	4	6	3	4	7	1	4	3	3	0	0	3	0	0
Dossiers accepted for assessment	11	12	3	10	43	13	9	4	17	15	8	3	14	8	5	3

HIV: human immunodeficiency virus; TB: tuberculosis; MA: malaria; and RH: reproductive health.
Number of rejected/cancelled dossiers during the same period has also been included.

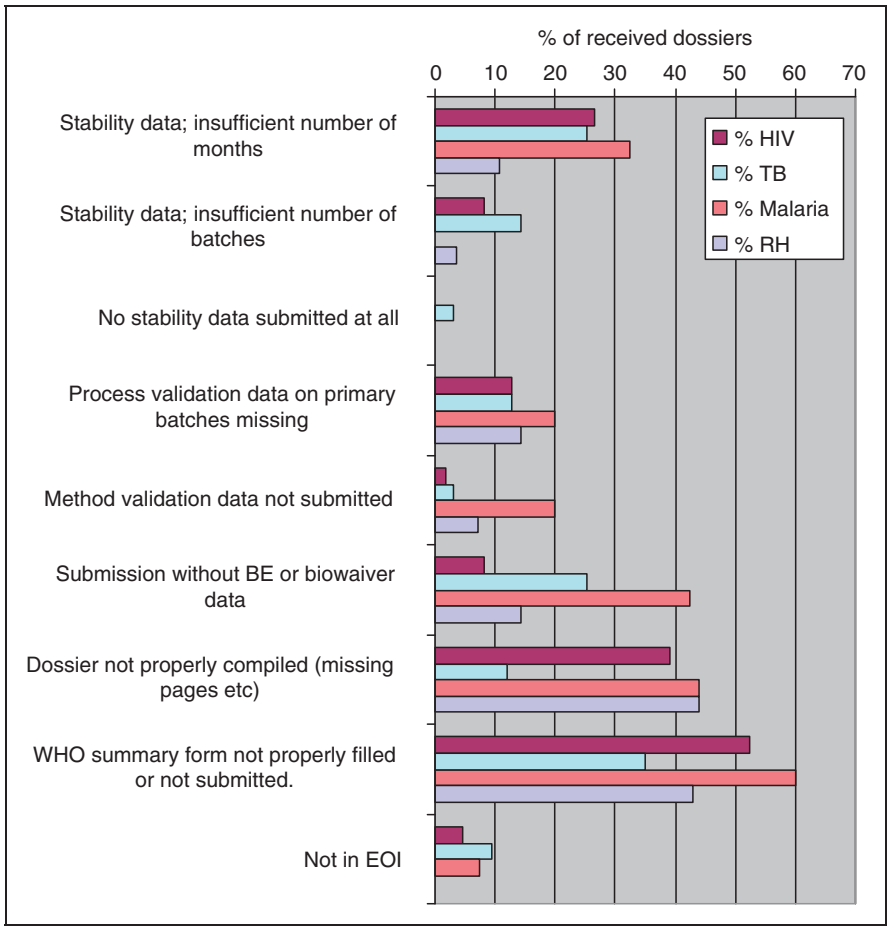

Figure 1. Deficiencies in generic product dossiers as observed during screening presented as percentage dossiers with a certain deficiency per therapeutic area.
HIV: human immunodeficiency virus; TB: tuberculosis; RH: reproductive health; BE: bioequivalence; EOI: expression of interest; and WHO: World Health Organization.

assessment could commence and nine were pending assessment as at the end of December 2010. Therefore, in total, 162 dossiers with a quality and/or efficacy/safety assessment report were available for analysis (79 HIV, 44 TB, 23 MA and 16 RH dossiers).

For the quality part, 147 reports were available for analysis (74 HIV, 42 TB, 18 MA and 13 RH). Most of the 147 quality assessment reports concerned tablet or capsule dosage forms −64 (86%) of HIV, 37 (88%) of TB, 14 (78%) of MA and 7 (54%) of RH dossiers. The remaining dossiers were for injectable preparations −3 (4%) of HIV, 5 (12%) of TB, 4 (22%) of MA and 6 (46%) of RH dossiers. Oral solutions/suspensions accounted for 7 (9%) of the HIV dossiers.

For the efficacy/safety part, 151 were reports available for analysis (76 HIV, 42 TB, 20 MA, 13 RH dossiers). Out of the 151 reports, 3 HIV, 5 TB and 3 RH reports concerned biowaiver applications for injectable products administered as solution. These were all considered acceptable during the first round of assessment, as were two HIV reports (biowaiver applications for oral solutions).

The quality and efficacy/safety parts of the same dossier are generally assessed at different time points, which may explain the absence of one of the two types of assessment reports for any given dossier.

The deficiencies observed during assessment are shown in Figures 2 (quality) and 3 (efficacy/safety).

In Figure 3, deficiencies encompass study design/administration (the first category on the *x*-axis of the graph), the clinical portion of the study (categories 2–5), bioanalysis (categories 6 and 7) and the statistical/pharmacokinetic analysis (categories 8 and 9). The final category on the *x*-axis (auditing/monitoring) falls across categories as all the data should have been audited.

The status, as of the end of December 2010, of the 178 dossiers accepted for assessment is presented in Table 2.

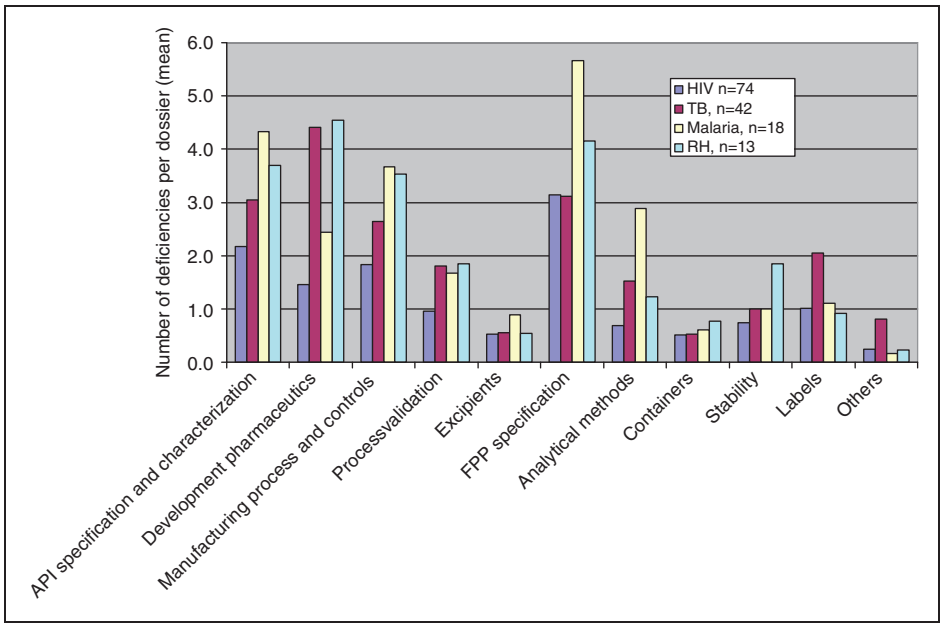

Figure 2. Deficiencies observed in generic product dossiers on the assessment of the quality (chemistry–pharmaceutical) part of the dossier, presented as the mean number of quality deficiencies per dossier and therapeutic area, by each of the 10 main categories.
Deficiencies are related to incomplete or incorrect information provided for the identified category.
HIV: human immunodeficiency virus; TB: tuberculosis; RH: reproductive health; API: active pharmaceutical ingredient; and FPP: finished pharmaceutical product.

Discussion

To our knowledge, this is the first comprehensive review of the quality and efficacy/safety portions of generic product dossiers, originating from pharmaceutical companies in emerging markets, and comparison of dossier deficiencies across four critically important therapeutic areas. Similar studies by USFDA and EMA investigated quality and/or efficacy/safety deficiencies in ANDAs or new drug applications, but did not indicate the therapeutic areas studied, nor the origin of the dossiers.[3–9]

Screening

Of the submitted 245 dossiers, 45 (18%) were rejected either at first screening, i.e. if the product was not invited to the programme or later due to the applicant's failure to respond to the PQP queries in a timely fashion (maximum 1 year) (Table 1). The proportion of rejected dossiers was found to be higher for MA (34%), RH (26%) and TB (20%) than for HIV (10%). Major deficiencies, such as inadequate stability data, incomplete or missing process and analytical validation data or missing BE data, resulting either in delayed acceptance or ultimate rejection of the dossiers, were more frequent in MA and TB dossiers (Figure 1).

Deficiencies such as improperly compiled dossiers, missing dossier pages or incomplete WHO summary forms were frequent across all therapeutic areas. Such deficiencies, although not a reason for non-acceptance or rejection of a dossier, are significant in delaying the start of the assessment of the dossier.

Assessment

The review of the assessed generic product dossiers submitted to the WHO Prequalification of Medicines Programme during April 2007 to December 2010 revealed considerably more critical quality-related deficiencies in TB, MA and RH dossiers compared to HIV ones (Figure 2). The same was true for the efficacy/safety part of the dossiers, in that the most critical deficiencies such as an incorrect study design, the use of an unacceptable comparator, or the failure to include a study, occurred considerably more frequently in the TB, MA, and RH dossiers than in the HIV ones (Figure 3).

Quality

As shown in Figure 2, deficiencies related to API and FPP specifications and manufacture of the FPP were the most frequent ones. This is similar to EMA findings.[3] The type of deficiencies noted below

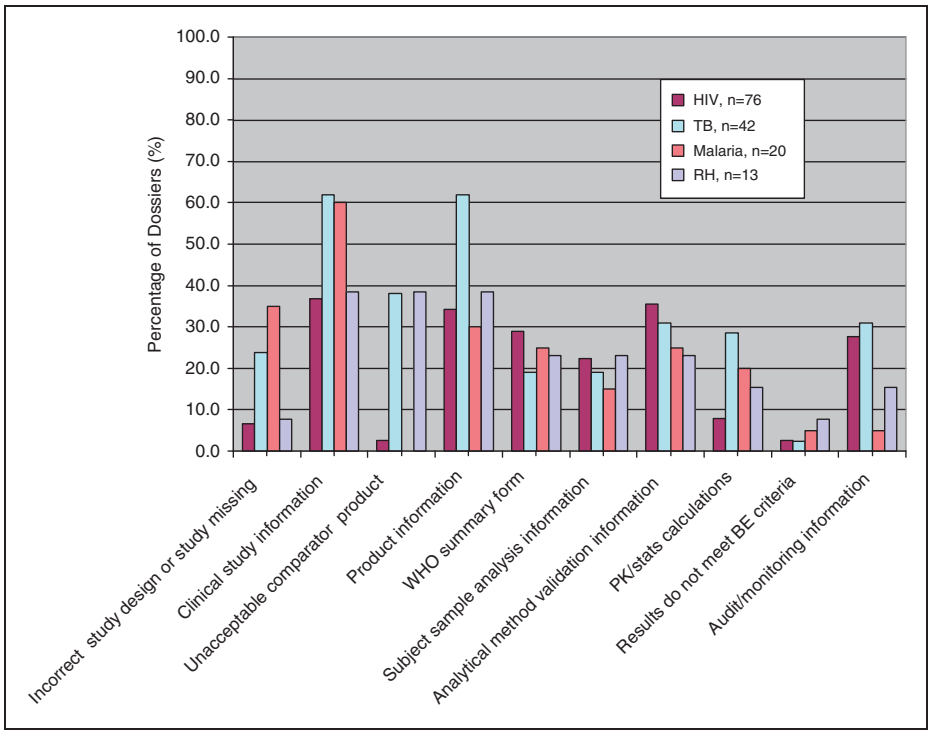

Figure 3. Deficiencies observed on the assessment of the efficacy/safety (i.e. BE/biowaiver) part of the dossier, presented as percentage of the total number of dossiers surveyed that contained each identified deficiency, per therapeutic area and by each of the four main categories.
Unless otherwise specified, deficiencies are related to incomplete or incorrect information provided for the identified category.
HIV: human immunodeficiency virus; TB: tuberculosis; RH: reproductive health; BE: bioequivalence; PK/stat: pharmacokinetic/statistical; and WHO: World Health Organization.

Table 2. Status of dossiers as of the end of December 2010 (only dossiers accepted for assessment; numbers and percentage of total within each therapeutic area)

	Cancelled	%	Under assessment	%	Prequalified	%	Total
HIV	15	18	42	49	28	33	85
TB	4	8	42	88	2	4	48
MA	7	28	16	64	2	8	25
RH	11	55	9	45	0	0	20

HIV: human immunodeficiency virus; TB: tuberculosis; MA: malaria; and RH; reproductive health.

is likewise similar to that reported by USFDA and EMA.[3–7]

API specification and characterization. There were fewer deficiencies in HIV dossiers as compared to other therapeutic areas (Figure 2). Inadequate data or information on physico-chemical characteristics of the API, missing or inadequate control on key parameters, such as particle size distribution (PSD) or inadequate control of impurities, and batch analysis data for the API batches used in the submission/exhibit batches were less frequent in HIV dossiers (range 11–24% of HIV dossiers with each of the above deficiencies) than TB (range 26–42%), MA (range 33–67%) or RH dossiers (range 24–69%) (data not shown). This may be due to a combination of availability of public information such as public assessment reports for HIV comparator products, the greater stringent regulatory authority (SRA) experience amongst HIV manufacturers and the fact that many of the HIV manufacturers produce their own APIs.

MA APIs are often water insoluble, which may contribute to the frequent deficiencies in MA dossiers. In the case of RH dossiers, the frequent deficiencies may be related to content uniformity issues, requiring additional controls.

For water-insoluble APIs, the rate of dissolution/solubility and the subsequent absorption of the active

ingredient depends on the physico-chemical properties of the API. Consequently, if different batches of API exhibit different polymorph forms or different PSDs, it may result in variable absorptions, possibly influencing the efficacy and/or safety of the product. Needless to say, if the active ingredient contains more impurities, these may be carried over to the final product and result in exposure of the patient to potentially toxic levels of impurities. API-related impurities should therefore be controlled or their levels should be limited to an acceptable or safe level.

Development pharmaceutics. As noted in Figure 2, the number of deficiencies in TB and RH dossiers was considerably higher compared to HIV and MA dossiers. Common deficiencies such as missing or inadequate data on API–API/API–excipient compatibility, insufficient information on selection and optimization of formulation and process parameters, missing or incomplete comparative dissolution profile data, inadequate data on qualification of proposed container closure system and absence of justification and supporting data for overages and score lines were observed in higher numbers in TB (range 26–50%) and RH dossiers (range 0–77%) compared to HIV (range 4–26%) and MA dossiers (range 6–22%). Presence of such deficiencies indicates that the manufacturer is not in control of the quality attributes of the product. In such cases, batch-to-batch quality variability is likely, with possibly variable treatment outcome.

Since most of the TB and RH products are not new to the manufacturers, generation of development data was not done in consideration of the current guidelines. Such incomplete study reports raise questions which may be addressed by the submission of a detailed annual product review for several production size batches. It is noted that all RH dossiers except one were submitted by manufacturers with limited or no SRA experience.

Manufacturing process, controls and process validation. There were a higher number of deficiencies for MA and RH dossiers compared to HIV dossiers, as illustrated in Figure 2. Common deficiencies were observed across the therapeutic areas, including HIV (range 4–34%), TB (range 12–50%), MA (range 11–66%) and RH (range 8–38%) dossiers. These deficiencies were related to missing executed and blank records, inadequate description of equipments, process parameters and end-point determination, inadequate description of sterile processes, unsatisfactory in-process tests and their frequency or acceptability of intermediate product specification. Also observed were missing protocols for process validation on production batches, inadequate sampling and testing plan and absence of data to support hold times for intermediate products (ranges HIV 14–22%, TB 19–36%, MA 17–39% and in up to 69% of RH dossiers). It is of note that 50% of the reviewed MA and RH dossiers were either compiled as a translated dossier or concerned injectable dosage forms for which the manufacturing process and its related records are required to be more detailed than for solid or oral liquid dosage forms. This may contribute to the overall higher number of deficiencies in MA and RH dossiers (Figure 2). Moreover, the RH manufacturers studied seemed to have limited SRA experience, in particular of SRA good manufacturing practice (GMP) inspections. Satisfactory documentation of manufacturing process records and execution of process validations is directly related to the level of GMP compliance.

Again, deficiencies with respect to the manufacturing process, controls and its validation may lead to variability in batch-to-batch quality, which could influence the product's in vivo performance. It is essential that the manufacturer identifies and controls the details of the process parameters, equipments, end points and in-process tests. Such controls ensure production of batches with uniform and consistent quality.

Excipients. Commonly observed deficiencies such as lack of identification tests for colourants/flavours, failure to submit supporting certificate of analysis and failure to submit the necessary TSE/BSE (transmissible spongiform encephalopathy/bovine spongiform encephalopathy) free certification for excipients of animal origin showed no obvious difference between the therapeutic areas (Figure 2 and data not shown). As mentioned above, most of the reviewed dossiers were for immediate-release tablets, capsules or solutions. Excipients used in such dosage forms are well established and there are readily available pharmacopoeial specifications across therapeutic areas.

FPP specification and analytical methods. This category represented the majority of deficiencies in terms of numbers. Overall, the deficiencies in TB and HIV dossiers were fewer compared to MA and RH product dossiers (Figure 2).

Deficiencies such as absence of additional identification test for active ingredients, unjustified/unacceptable dissolution limits, unjustified limits for moisture content and insufficient supporting data for microbial skip testing proposals tended to be more frequent in MA dossiers (39–72%, mean 60%) compared to other therapeutic areas but were common also in HIV (range 16–50%, mean 33%), TB (range 22–71%, mean 39%) and RH (range 8–38%, mean 23%) dossiers. With regard to control of degradation products, there

were less frequent deficiencies in HIV (34%) and TB (29%) dossiers compared to MA (72%) and RH (46%) dossiers.

Absence of certain tests or unacceptably wide acceptance limits suggest potential batch-to-batch variability. For example, wide dissolution limits may allow marketing of batches with significantly different dissolution results compared to the batch used in clinical or bio-studies. Such differences may translate to differences in in vivo bioavailability. Similarly, if the acceptance limits for impurities are not sufficiently tight, batches with higher impurity contents may be marketed, leading to potential toxicity.

Concerning validation of analytical methods, most deficiencies related to inadequate demonstration of specificity, quantitation limits, repeatability and accuracy for assay, dissolution and related substance methods were more frequent in MA dossiers (range 55–66%) compared to HIV (range 5–18%), TB (range 26–35%) and RH (range 8–46%) dossiers.

Deficiencies in terms of validation will put in question the validity or reliability of the analytical method used to test the quality of the product. Unreliable test results means that the efficacy/safety profile of the product cannot be assured.

Presence of public assessment reports on comparator products, well-defined API specifications along with well-executed development studies and experience with SRA submission enable the development of FPP specifications, which may explain the relatively low number of deficiencies for HIV dossiers. In respect of TB, there is an increasing availability of monographs for first-line TB products in USP, BP and PhInt. For MA products, there were only a few pharmacopoeial monographs for artemisinin-based FPPs until recently and manufacturers were expected to develop and validate their own specifications and analytical methods. In the area of RH products, despite the existence of monographs for some of the products, tests such as related substances and dissolution were not included. In such cases, manufacturers will be expected to develop in-house test methods. Most of the RH manufacturers studied, due to limited SRA experience, tend to limit their specifications to the minimum pharmacopoeial requirements. The absence of analytical validation data for related substances and dissolution may explain the fewer questions on analytical method validation for RH dossiers.

Container closure systems. The number of deficiencies in this category was similar across the therapeutic areas (Figure 2). Exclusion of identity testing from primary container specifications was the major deficiency observed most frequently in RH dossiers (54% of the dossiers) but was also seen in HIV (24%), TB (35%) and MA (33%) dossiers. Containers with immediate contact with the product should be confirmed to be non-toxic as there could be migration of substances from the container to the product. Thus, absence of control of the identity (nature and quality) of the primary container components may allow use of unapproved potentially toxic containers.

Stability data. Deficiencies were of similar frequency across the HIV, TB and MA dossiers (Figure 2). Failure to provide adequate discussion on observed trends, variability, lack of mass balance and out-of-specification results was observed in 50% of the MA dossiers (21% of HIV, 22% of TB and 37% of RH dossiers). An additional common deficiency that was observed in 75% of RH dossiers was failure to include critical stability indicating parameters such as related substances and dissolution. The RH product manufacturers studied tended to design their stability studies based on minimum test parameters as specified in pharmacopoeial monographs which do not necessarily include tests for related substances or dissolution and therefore did not comply with stringent regulatory requirements.

A pharmaceutical product should have a certain shelf life (validity period) within which the approved quality characteristics and ultimately the approved safety and efficacy profiles remain acceptable. If a batch of the FPP fails to maintain its approved quality characteristics after release for marketing or distribution, then it is no longer possible to assure the efficacy/safety profile of that batch. Stability data collected from studies on a certain number of batches are used to extrapolate a shelf life for every future batch. It is essential that such stability results are rigorously analysed and discussed to make sure that results are confidently extrapolated to future batches.

Product labelling. Quality-related information included in the summary of product characteristics/patient information leaflet and outer and immediate container labels are assessed as part of the quality assessment of the dossier. Common deficiencies were failure to include storage statements that reflect the stability results, failure to include appropriate instruction on dosage administration, failure to indicate the full excipient list and failure to include complete information on the nature and contents of the product container.

Other/miscellaneous quality deficiencies. Other/miscellaneous deficiencies concerned discrepancies in data provided in the WHO summary form for quality

(i.e. pharmaceutical quality information form) as compared to the submitted dossier, missing product samples or submission of samples which did not represent the product features proposed in the dossier.

Efficacy/safety

Study design. As noted in Figure 3, TB and MA dossiers were more often deficient in this area than HIV or RH dossiers. Earlier, MA dossiers tended to include information related to some limited clinical trials or clinical experience with the proposed product. These trials were not sufficient to establish the efficacy/safety of the proposed product without comparison to a comparator product and, if the trials were comparative in nature, they were not sufficiently robust and/or were not properly designed to detect product performance differences. Regarding TB dossiers, many of the TB products are fairly old products and the data provided in support of some of these products were found to be deficient in relation to the current guidelines. These issues were not observed with the HIV or RH product dossiers.

Deficiencies with respect to the study design will question the reliability of the final pharmacokinetic results and BE and ultimately the therapeutic equivalence of the proposed formulation to the acceptable comparator product.

Clinical study information. In keeping with the findings in the quality part of the dossier, overall, the efficacy/safety portion of HIV dossiers contained fewer deficiencies than dossiers submitted in the TB and MA categories. This is highlighted in Figure 3 where it can be seen that 60% of submitted TB and MA dossiers, contained deficiencies in the information provided in support of the clinical portion of the studies submitted, while the percentage of HIV (or RH) dossiers containing significant deficiencies in the information related to the clinical portion of studies was lower (37%). A notable proportion of the deficiencies found in the clinical study information were related to correctable issues such as the failure to provide complete information on the drug products that were employed in the study or failure to provide adequately prepared WHO summary forms for BE, i.e. the BE trial information form. Such deficiencies were typically correctable and hence delayed the acceptance of the efficacy/safety portion of dossiers but did not prevent it.

There were other deficiencies related to the design and conduct of efficacy/safety studies that resulted in dossiers being found unacceptable. An unacceptable dossier does not necessarily indicate that the proposed FPP itself is unacceptable; it may just be that the information submitted does not adequately establish the safety and efficacy of that product. For example, a small percentage of dossiers in each treatment area included studies whose data did not meet the BE acceptance criteria. Such results do not prove that the proposed product and comparator are inequivalent, but they fail to prove the objective, BE (and ultimately therapeutic equivalence).

In addition to the submission of incorrectly designed studies or the failure to submit a study at all, other deficiencies were noted which precluded the useful evaluation of the proposed FPP's performance. A significant number of TB and RH dossiers included studies that employed an unacceptable comparator product. In all these cases, the efficacy/safety portion of the dossier was unacceptable as an assessment of the proposed product's performance could not be completed. BE is meaningful only when the comparator product was approved based on clinically established safety and efficacy information. The tendency for this deficiency to occur most frequently with TB and RH products may be related to the age of these products, i.e. they tend to be older products than those falling into the HIV and MA areas, and hence, studies conducted with local comparator products conducted originally for purposes other than submission to this programme tend to be more common.

Bioanalytical information. This category was divided into two subcategories: information related to the analysis of the clinical subject samples and analytical method validation information.

As illustrated in Figure 3, dossiers in all therapeutic areas contained deficiencies in both these subcategories. With regard to subject sample analyses, deficiencies related to calibration data, quality control data and the selection of samples for repeat analyses were all observed in 5–10% of the dossiers for all therapeutic areas, with the exception that issues related to the selection of samples for repeat samples were noted in approximately 15% of the RH dossiers (data not shown). Incomplete documentation with respect to subject sample analyses, an issue that would delay completion of the dossier assessment, was observed in between 7% (for HIV dossiers) and 15% (for MA dossiers) of the submitted dossiers (data not shown).

With regard to information related to the analytical method validation, seriously deficient or no method validation was provided for between 7% (for HIV dossiers) and 19% (for TB dossiers) of the submitted dossiers (data not shown). It is interesting to note that none of the RH dossiers were considered to possess seriously deficient or no method validation

information, although the method validation information in 15% of the RH dossiers was considered to be unclear or inconclusive in some respects. The most significant deficiencies in the submitted method validation information for all the treatment categories were related to stability data. Between 15% (for MA and RH dossiers, respectively) and 29% (for HIV dossiers) of the submitted dossiers were deficient in stability data (data not shown). The frequent deficiency was related to inadequate or missing long-term storage stability data under the correct study conditions for plasma samples containing the moiety of interest. It is likely that this deficiency is more commonly present in the dossiers related to the HIV and MA products, because, again, they tend to be newer products relative to the TB and RH products and the data were still in the process of being generated at the time of dossier submission.

The bioanalytical deficiencies highlighted above are similar to those identified as the most common deficiencies in ANDA applications to USFDA.[8,9]

Needless to say, the above deficiencies, unless corrected or clarified, question the acceptability of the final pharmacokinetic results and ultimately the therapeutic equivalence of the proposed product.

Pharmacokinetic/statistical analyses. Dossiers from all therapeutic areas contained some deficiencies related to the pharmacokinetic/statistical analysis of the study data, although a higher percentage of these deficiencies were noted in TB dossiers than in the other therapeutic areas. The majority of the deficiencies in this area in the TB dossiers were related to insufficient information being provided in order to understand the procedures employed by the investigators and a failure to discuss the observed results in the context of other data available from studies related to the pharmacokinetics/bioavailability of the moiety of interest. The RH dossiers were again somewhat unique in that 15% of the dossiers included incorrect pharmacokinetic/statistical calculations that required revision and re-calculation. This deficiency was observed in 10% or less of the dossiers in other treatment categories (data not shown).

Audit/monitoring information. Approximately 30% of the dossiers submitted in the HIV and TB treatment categories were found to be deficient in the information provided in relation to the auditing and monitoring activities that took place in relation to the studies undertaken (Figure 3). This factor was also found to be the case in 15% of the RH and 5% of the MA dossiers (Figure 3). Although in some cases it was found that the level of monitoring that occurred during the study was minimal, in most cases, sufficient auditing/monitoring did occur.

Status of dossiers as of the end of 2010

Table 2 presents the status, as of the end of December 2010, of the 178 dossiers accepted for assessment. A total of 32 (18%) had been prequalified, 109 (61%) were under assessment and 37 (21%) had been cancelled/withdrawn. At the end of Dec 2011 (data not shown), the number of prequalified products had increased to 60 (HIV: 49, TB: 6, Malaria: 3 and RH: 2). The number of cancelled/withdrawn dossiers had increased from 37 to 54 (HIV: 22, TB: 9, Malaria: 11 and RH: 12).

Limitations of this study

The number of MA and RH dossiers in this material was relatively small. Due to the absence of a formalized screening procedure for dossiers submitted prior to April 2007, data from older dossiers could not be easily merged with data from more recent dossiers (post-April 2007). Dossiers submitted to the programme prior to April 2007 were therefore excluded. Further, since the quality of dossiers submitted to the programme has improved significantly since 2001 and assessment practices and guidelines (WHO and others) likewise have developed, a study of a more recent population of dossiers would better reflect current dossier related issues within the WHO Prequalification of Medicines Programme. RH is a new therapeutic area in PQP and the number of RH dossiers submitted has been low since their first invitation to PQP (late 2006). For all therapeutic areas, the dossier-related deficiencies were those identified following the first assessment of the dossier. The applicant's response to the issues raised was therefore not included in this review. Also, with respect to the API, only the API specifications used by the FPP applicant were included. Therefore, any additional issues identified as part of the assessment of the corresponding APIMF/DMF (drug master file) which may have affected the final acceptability of the API specification, such as control of additional impurities, have not been covered. For some of the efficacy/safety categories (Figure 3), the differences between the therapeutic areas may reflect the differences between contract research organizations (CROs) rather than manufacturers. However, certain deficiencies are less dependent on the CRO chosen and may thus better reflect differences between therapeutic areas (for example, availability of acceptable comparator product or incorrect study design).

Conclusion

In this review of generic product dossiers submitted to the WHO Prequalification of Medicines Programme during April 2007 to December 2010, there were considerably more quality-related deficiencies in TB, MA and RH dossiers compared to HIV dossiers, especially in the categories specification of APIs, development pharmaceutics, manufacturing method and FPP specifications. This may be related to the applicant's experience of interacting with SRAs, availability of information on comparator products, availability of pharmacopoeial monographs and the age of the product.

The deficiencies related to the efficacy/safety portion of the dossiers displayed a trend similar to that observed in the quality portion in that the most critical deficiencies, such as an incorrect study design, the use of an unacceptable comparator or the failure to include a study, occurred considerably more frequently in the TB, MA, and RH dossiers than in the HIV dossiers. Similarly, less critical but still important deficiencies in the clinical study information also occurred less frequently in the HIV dossiers than in the dossiers for the other therapeutic areas. Again, these findings may be attributable to the fact that the HIV products tend to be newer products than some of the other products, the TB and RH products, in particular, and hence, there are fewer old studies in existence for these products that may not have been designed to satisfy the requirements of the more SRAs and/or employed local comparators that do not meet programme requirements. Dossiers for all therapeutic areas showed a similar frequency for deficiencies related to the bioanalytical portion of the submitted studies. The most common deficiency in this area was the failure to provide complete study-relevant stability data.

The frequency of dossier-related deficiencies as determined on screening and assessment of the dossiers seemed to be inversely related to the number of the product dossiers that had been prequalified by the end of 2010 (Table 2).

The results of this study stress the need for continued capacity building of local generic manufacturers, further development of pharmacopoeial monographs by WHO (PhInt) and other pharmacopoeial commissions, not least to promote the development of generic products, as well as development of new guidelines (WHO guidelines for development of generic and paediatric products and a technology transfer guidance document are currently being finalized).

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Conflict of interest

The authors have no conflicts of interest that are directly relevant to the content of this article. The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of, WHO or Health Canada.

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