

Assessment of active pharmaceutical ingredients in drug registration procedures in Pakistan: implications for the future

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Introduction: There are concerns over the quality of generic medicines in Pakistan. This is due to perceived non-compliance with good manufacturing practice (GMP), whereby the quality of the raw materials is not being assessed. If not addressed, this will impact on the potential for generics exports from Pakistan, as well as on patient care. Consequently, there is a need to assess the current assessment and regulatory situation in Pakistan and to recommend a way forward that ensures the future quality of products.

Objective: To assess the quality of the raw materials that are either imported to, or manufactured in Pakistan, that are then used to produce a leading analgesic (ibuprofen). As part of the assessment, the presence and levels of impurities will be determined. Subsequently, the findings will be used to recommend potential regulatory changes to improve patient care.

Methods: The quality of 27 sourced raw materials and the reference product were assessed using a variety of quality assessment methodologies, including assay tests, and infrared spectroscopy and UV-spectrophotometry. The calculated values were then compared to values documented in the Certificate of Analysis (CoA), and high performance liquid chromatography (HPLC).

Results/Discussion: All but one sample passed the spectroscopy identification tests. However, 81.5% of samples failed to comply with pharmacopoeia assay limits. There were also concerns with the use of HPLC methods used to assess the quality of raw materials, and over the fact that assay values obtained were not the same as those listed in the CoA. In addition, where manufacturers had concerns over the amount of ibuprofen in the raw material, rather than rejecting the product, they typically used higher quantities to make up any shortfall.

Conclusions: The results of this study demonstrate that there is an urgent need to improve the registration process for generic products in Pakistan. This should include implementing Common Technical Documents (CTDs) based on international standards. In this way, we will see generics being produced that result in improved patient care and that have potential for export from Pakistan.

Keywords: API (active pharmaceutical ingredient), Drugs Regulatory Authority, generics, ibuprofen, Pakistan

Introduction

The pharmaceutical market in Pakistan was worth approximately US\$2.3 billion in 2014 [1]. At present, Pakistan produces a variety of medicines and meets approximately 90% of the demand for domestic finished products. However, currently Pakistan only produces a limited amount of the active pharmaceutical ingredients (APIs) needed for medicines consumed in Pakistan [2], with more than 90% of raw materials/APIs coming from China and India.

There are concerns over the quality of medicines manufactured in Pakistan due to perceived non-compliance with good manufacturing practice (GMP) requirements outlined by pharmaceutical manufacturers [3]. These include checks on the quality of APIs being used to produce oral tablets [3]. GMP requirements are included in the Drug (Licensing, Registering and Advertising) Rules (Schedule-B II), which were enacted in Pakistan in 1976 [4]. However, since then, GMP and other registration requirements have not been updated [5]. This means that there have been no updates or revisions following the creation of international standards or World Health Organization (WHO) guidelines [6]. With over 1,200 registered medicines and over 80,000 registered drug products in Pakistan [5], coupled with physician concerns over the safety and efficacy

of lower cost generics, the country sees high levels of prescribing of originator products [5, 7, 8]. This is a public health concern as self-pay for medicines in Pakistan is widespread [9] and therefore there are implications for affordability and subsequent adherence rates, especially for treatment of chronic diseases affecting the lower paid [10–12]. Patient care is not compromised with generic medicines that meet agreed quality standards, including bioequivalence levels, across a wide range of disease areas [13–19]. Concerns over generic immunosuppressants are also reducing [20].

There is inconsistency between the information to be included in application dossiers required for authorizing a medicine in Pakistan by the Drugs (Licensing, Registering and Advertising) Rules, 1976, and those stated in the Drug Regulatory Authority of Pakistan (DRAP) Act, 2012 [21]. In this Act, Schedule-I states that the pharmaceutical dossier should include a set of the following documents for submission that give all information on the technical aspects of a product's manufacture:

- Master formula
- All ingredients both active pharmaceutical ingredients and inactive excipients added with their safety profile data
- Complete manufacturing procedure of the drug, biological or medical device

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- d. Quality control steps and procedures at each level of raw material selection, in-process testing, finished drug testing and stability testing
- e. Clinical trial data and published reports about the safety and efficacy of the drug
- f. Complete details of manufacturing plant and equipment, quality control laboratories and equipment
- g. Warehouse capacities and facilities; details of human resources available and the latest cGMP (current good manufacturing practice) report shall also be part of this document set
- h. Any other information required by the Registration Board for establishing the safety, efficacy, bioavailability, bioequivalence, or biosimilarity of the drug.

Section 7 (c) (ix) of the DRAP Act, also emphasizes the systematic implementation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), WHO and US Food and Drug Administration (FDA) guidelines [3, 6, 22]. All of these guidelines suggest that application for the registration of medicines in a country should follow an internationally harmonized format known as the Common Technical Document (CTD). The CTD consists of five modules [23]:

- Module 1 Region-specific Administrative information
- Module 2 Quality overall summary (Overview and summary of modules 3 to 5)
- Module 3 Chemistry manufacturing and Controls (Quality)
- Module 4 Non-clinical/Preclinical (Safety)
- Module 5 Clinical (Efficacy)

However, despite many developing countries implementing such standards, these standards are not implemented in Pakistan. The lack of implementing such standards demonstrates the continued weaknesses of this registration process [5].

The quality of medicines in Pakistan is of major concern. DRAP is currently unable to effectively check the quality of all APIs and finished products through the available surveillance testing laboratories that are under governmental control. These materials are typically only tested to be quantified, and not for the identification of impurities, nor do they undergo any other pharmacopoeia tests. In addition, most of the laboratories involved in conducting these tests appear to contain out-dated instruments and materials, and there are concerns over levels of staff training and availability, as only a limited number of staff have been hired in recent years. This is despite such regulations being included in current laws [24].

The medicine registration process in any country is key to the availability of medicines that meet agreed quality targets. Concerns over the quality of generics produced in Pakistan is currently resulting in low exports [25] and impacting on patient care, especially for patients with chronic diseases.

There are also concerns that the basic and semi-basic industry involved in the manufacture of raw materials in Pakistan has not flourished due to unfavourable policies towards the protection or security of businesses. This is reflected by the fact that only 33 manufacturing units are currently involved in basic or semi-basic manufacturing of pharmaceuticals in Pakistan [26]. This

compares with approximately 600 active licensed manufacturers of finished products in Pakistan [27]. In addition, among these 33, only seven manufacturing units currently appear active further demonstrating problems with current policies [26].

Objective

Considering these concerns, this study has assessed the quality of APIs in Pakistan and seeks to use the findings as a starting point for suggesting improvements in the registration process for oral generic tablets. We chose ibuprofen for our study in view of the extent to which it is prescribed in Pakistan, which is 12% by value of the analgesic market. The analgesic market currently has a growth of 20% per annum [28]. In addition, APIs of ibuprofen are produced both locally and imported. For ibuprofen, there are specific concerns relating to potential impurities in the light of pharmacopoeia specifications. The findings will subsequently serve as a guide to suggest improvements for the pharmaceutical drug registration process in Pakistan, to ensure good quality, safe, effective and affordable medicines are being produced that will help improve patient care in Pakistan, and potentially boost exports.

Methods

Collection of ibuprofen API samples

Twenty-seven samples of ibuprofen APIs used by manufacturers in Pakistan were obtained, together with their Certificate of Analysis (CoA). The CoA contained details regarding the results of tests and their values and limits (including assay values) of relevant batches, as well as information about the manufacturer. The US Pharmacopoeia (USP) reference standard ibuprofen was obtained from Abbott Laboratories, Pakistan (originator manufacturer of ibuprofen). Coding was undertaken on all collected samples, with all samples stored in closed containers. Desiccators were used to avoid moisture absorption.

Quality assessment

The quality assessment of the ibuprofen samples was performed using the following methods:

1. Identification test

All samples were identified using the following two methods:

- FTIR (Fourier Transform Infrared) Spectroscopy. In this method, dry samples were used and placed in the instrument after cleaning with methanol. The HazMatID (Smiths Detection, USA) instrument was used for this purpose. The results from the HazMat (FTIR analyser) were interpreted from percentage resemblance, rather than being represented as concordant or not concordant with the reference spectrum.
- UV-Spectrophotometry. The UV identification test for ibuprofen is the ratio of the absorbance at 264 nm and 273 nm, reported again as percentage difference to the USP Reference Standard, and not as a pass/fail.

For all API samples and the USP Reference Standard (Abbott Laboratories, Pakistan), the solutions were prepared in 0.1 N Sodium Hydroxide with a concentration of 0.025 g per 100 mL, equivalent to 250 µg per mL of ibuprofen. Respective absorptivities at 264 nm and 273 nm on the anhydrous basis were noted.

For the UV-Spectrophotometer limits, the absorptivities were calculated on an anhydrous basis, and should not differ by more than 3.0% at 264 nm and 273 nm, as per USP limits.

Table 1: Chromatographic conditions/system requirements

Instrument	Ultra fast HPLC SIL-30AC
Analytical column	Column with L1 packing and dimensions of 4.6 mm × 25 cm
Mobile phase	Chloroacetic acid (4.0 g) dissolved in water (400 mL) and adjusted to a pH of 3.0 with ammonium hydroxide. Acetonitrile (600 mL) was added, filtered and degassed
Flow rate	2.0 mL per minute
Injection volume	5 µL
Detector	UV at 254 nm
HPLC: high performance liquid chromatography.	

The testing of ibuprofen against USP specifications was undertaken in one of Pakistan's 'Appellate Laboratory', known to perform to the highest standards. The utilization of an USP approved laboratory to undertake the testing has significance in terms of the reliability of the results, negating the need to test the samples in other USP international laboratories in either Brazil or China or India.

2. Assay test

USP specifications mention the following limits for assay testing, 'Ibuprofen (Active Pharmaceutical Ingredient) contains not less than 97.0 per cent and not more than 103.0 per cent of C₁₃H₁₈O₂, calculated on the anhydrous basis' [29]. The USP only documents one related or impurity substance, this is in contrary to the British Pharmacopoeia specifications where 18 substances are mentioned. However, the identification and characterization of related or impurity substances is out of the scope of this paper.

The Assay Test procedure

Mobile phase

Chloroacetic acid (4.0 g) was dissolved in water (400 mL) and then adjusted to a pH of 3.0 with ammonium hydroxide. Acetonitrile (600 mL) was added, then filtered, and degassed. Amendment or modifications were done as per the requirements of *System Suitability*.

Preparation of standard solution

A solution with concentration of about 12 mg per mL was prepared by dissolving USP Ibuprofen RS (accurately weighed) in Internal Standard Solution.

Assay preparation

1200 mg of ibuprofen, accurately weighed, was transferred to a 100 mL volumetric

flask, diluted with Internal Standard Solution to volume, and mixed. Table 1 contains details of the chromatographic conditions.

The L1 column packing used was Octadecylsilane C18 as C18 is generally more retentive than C8.

Test for system suitability

The peak response was recorded after repeated injections of five to six consecutive standard solutions before injecting the sample solutions. This was repeated after completion of work, to observe the consistency of performance of the system.

Acceptability criteria

The qualification criteria for the system suitability test was that there should be less than 2% Relative Standard Deviation (RSD)

Table 2: Results of FTIR Spectroscopy and UV-Spectrophotometry at 264 nm and 273 nm

S. No.	Sample name	Percentage resemblance through FTIR	Absorption at 264 nm	Percentage difference (%)	Absorption at 273 nm	Percentage difference (%)
1	USP Standard	100	0.450	–	0.350	–
2	IBU-1	99.8	0.450	0	0.354	0.4
3	IBU-2	99.7	0.446	0.88	0.349	0.1
4	IBU-3	98.8	0.465	1.5	0.365	1.5
5	IBU-4	99.3	0.477	2.7	0.379	2.9
6	IBU-5	99.4	0.433	1.7	0.342	0.8
7	IBU-6	99.6	0.459	0.9	0.352	0.2
8	IBU-7	99.2	0.436	1.4	0.337	1.3
9	IBU-8	99.7	0.450	0	0.351	0.1
10	IBU-9	99.6	0.445	0.5	0.352	0.2
11	IBU-10	99.3	0.460	1.0	0.357	0.7
12	IBU-11	99.6	0.449	1.0	0.354	0.4
13	IBU-12	98.6	0.448	0.2	0.348	0.2
14	IBU-13	96.9	0.425	2.5	0.329	2.1
15	IBU-14	87.0	0.409	4.0	0.319	3.1
16	IBU-15	98.5	0.439	1.1	0.344	0.6
17	IBU-16	97.2	0.430	2.0	0.335	1.5
18	IBU-17	98.9	0.448	0.2	0.339	1.1
19	IBU-18	99.0	0.435	2.0	0.335	1.5
20	IBU-19	98.1	0.484	3.4	0.363	1.3
21	IBU-20	97.7	0.441	0.9	0.343	0.7
22	IBU-21	97.9	0.429	2.1	0.338	1.2
23	IBU-22	96.8	0.433	1.7	0.337	1.3
24	IBU-23	95.0	0.428	2.2	0.335	1.5
25	IBU-24	92.5	0.450	0	0.350	0
26	IBU-25	96.2	0.461	1.1	0.365	1.5
27	IBU-26	93.2	0.434	1.6	0.334	1.6
28	IBU-27	94.0	0.417	3.3	0.323	2.7

FTIR: Fourier Transform Infrared; S. No.: Serial Number.

Table 3: Ibuprofen assay value

S. No.	Sample name	Percentage assay quantity	Assay value claimed in the CoA	Difference in assay value obtained experimentally compared to that claimed in CoA (%)
1	USP Standard	100	–	–
2	IBU-1	92.51	100.4	7.89
3	IBU-2	96.87	99.81	2.94
4	IBU-3	97.84	99.00	1.16
5	IBU-4	96.69	99.50	2.81
6	IBU-5	97.08	99.75	2.67
7	IBU-6	97.40	99.80	2.4
8	IBU-7	96.15	99.50	3.35
9	IBU-8	96.39	99.90	3.51
10	IBU-9	96.53	99.80	3.27
11	IBU-10	95.51	99.50	3.99
12	IBU-11	94.70	99.30	4.6
13	IBU-12	96.72	99.40	2.68
14	IBU-13	92.69	99.87	7.18
15	IBU-14	99.15	99.80	0.65
16	IBU-15	95.50	99.50	4
17	IBU-16	97.85	99.10	1.25
18	IBU-17	94.48	99.10	4.62
19	IBU-18	94.90	99.60	4.7
20	IBU-19	96.33	99.20	2.87
21	IBU-20	94.80	99.80	5
22	IBU-21	94.39	99.84	5.45
23	IBU-22	96.31	99.10	2.79
24	IBU-23	94.85	99.50	4.65
25	IBU-24	96.19	99.87	3.68
26	IBU-25	95.70	99.00	3.3
27	IBU-26	96.53	99.51	2.98
28	IBU-27	95.60	99.87	4.27

CoA: Certificate of Analysis; S. No.: Serial Number.

for five replicate injections of the standard solution, with not more than 2.5 tailing factors for the individual peaks.

Procedure

Equal volumes (approximately 5 µL) of the Standard preparation and the Assay preparation were separately injected into the chromatograph. Chromatograms were recorded and the response for the major peaks was measured.

The quantity of ibuprofen in mg was calculated using the formula: $100 C (RU/RS)$ where:

- *C* is the concentration, in mg per mL, of USP Ibuprofen RS in the Standard preparation; and

- *RU* is the peak response ratios obtained from the Assay preparation; and
- *RS* is the peak response ratios obtained from the Standard preparation.

Results

1. Identification test

Through FTIR (Fourier Transform Infrared) Spectroscopy:

Table 2 documents the percentage resemblance of the FTIR spectra of the 27 samples, to the USP standard spectrum. It also shows the percentage difference between the 27 samples and the USP standard spectrum, for the 264 nm and 273 nm peaks, recorded via UV-Spectrophotometry.

For measurements taken on the same day, precision ranged from 0.23% to 0.62%, and accuracy ranged from 99.6% to 100.3%. For measurements taken on different days, precision ranged from 0.24% to 0.52%.

2. Assay values

Table 3 documents the assay values of the 27 samples and the ibuprofen USP reference standard.

Discussion

The results reveal both positive and concerning aspects surrounding the APIs currently used in the production of generic ibuprofen tablets in Pakistan.

All samples, except sample IBU-14, passed the Identification test through FTIR and UV methods as per the requirements of USP specifications, see Table 2. Using the analytical methodology or assessment suggests that 96% API samples passed the test and can be approved and marketed as ibuprofen.

However, 22 out of 27 (81.5%) of the ibuprofen samples failed to comply with the USP assay limits, i.e. 97% to 103%. Interestingly, sample IBU-14 passed this test with highest percentage of assay value, i.e. 99.15%, see Table 3. IBU-14 also showed minimal difference in assay value to the values mentioned in the product CoA, see Table 3.

Secondly, one extra peak was noticed in the chromatograms of six (18.5%) of the samples, i.e. IBU-3, IBU-4, IBU-5, IBU-10, IBU-19 and IBU-25, at approximately the same time, i.e. between 3.1 to 3.3 minutes.

Thirdly, the comparison of assay values obtained using our methodology, versus those claimed by the manufacturer in their CoA, see Table 3, shows that none of the samples complied with the assay values claimed in their CoAs. Instead, three (11%) of the samples showed more than a 5% difference in assay value. In the majority of cases, the manufacturers of the finished products did not perform any testing on the API supplied. Instead, they typically rely on the CoA. This should be of concern to both regulators and manufacturers. Regulators in terms of the implementation of cGMP, while manufacturers should ethically and legally be

responsible to follow cGMP for their finished products. In cases where product manufacturers perform tests on the APIs, when assay values of API are found to be lower than the prescribed limits, instead of rejecting the raw material or API, they typically use higher quantities in the production of ibuprofen tablets based on their own calculations, which raises concerns over the quality of products (Hussein S 2016, personal communication, November 8).

Our findings show a general failure of the current system of drug regulation in Pakistan that surrounds the quality of APIs used for drug production. This is in line with previous publications [5]. This will negatively impact on the quality of finished generic products for use in patients and will potentially compromise patient care. The results also show that quality assessment of multiple source medicines should not rely on assay testing alone. Other pharmacopoeia tests are also important, especially in cases where the optical activity and the presence of genotoxic, and other impurities, have a critical impact or role regarding the efficacy, safety and quality of medicines. Here, the failing sample of ibuprofen (IBU-14) passed the assay test with the highest value, while the sample failed the identification test. This invites scientific discussion regarding the value of current assay testing for generics in Pakistan, see Table 2. The results suggest that IBU-14 was not a pure API of ibuprofen. Instead, it may contain related substances or impurities which have a very close structural resemblance to the API of ibuprofen, and the HPLC method used could not identify these or discriminate them from the actual API of the drug [30]. This is why the USP does not mention the use of the HPLC method for the identification testing of ibuprofen API. Consequently, the USP compendium of methods for the identification of ibuprofen API, i.e. the FTIR and UV-Spectrophotometer methods, should be used in the future to assess the content of APIs in Pakistan.

The extra peak in the chromatograms, at 3.1 to 3.23 minutes, is also an important observation. When samples IBU-3, IBU-4, IBU-5, IBU-10, IBU-19 and IBU-25 (18.5%) were investigated for their source of manufacturing, it was found these samples were procured from only three sources. Two were in Pakistan (B and H) and one was in India (C). Further appraisal revealed that all APIs purchased from sources C and H showed this extra peak at the same time range. This illustrates the necessity to perform prequalification studies to evaluate the quality of the API from pharmaceutical manufacturers, before turning the raw materials into finished goods. However, only two out of seven (approximately 29%) API samples purchased from source B showed this extra peak. These results need to be further investigated for the characterization of this peak through evaluation of the route of synthesis or method of manufacturing of the API in order that potential corrective and preventive measures can be suggested for the future. It seems that this extra peak may be due to residual solvent or impurities remaining in the API. However, this needs further investigating before any definitive statements can be made. We are aware that both the British Pharmacopoeia and European Pharmacopoeia include a test for related substances for ibuprofen, with 18 potential impurities listed in the British Pharmacopoeia. However, as mentioned previously, the USP mentions only one specific impurity.

Assessment of the drug registration process and requirements in Pakistan

In view of the findings regarding the assessment of the current procedures concerning the registration of medicines in Pakistan,

Box 1: Suggested technical requirements for registering medicines in Pakistan

1. Pharmaceutical Development Studies for establishment of a master formulation (Q-8 – ICH).
2. Stability studies (Q-1 – ICH).
3. Validation studies (for manufacturing method and analytical procedures).
4. Studies verifying suitability and establishment of specifications of packaging material/container closure system.
5. Indigenous clinical trials for new and imported drugs and/or bioequivalence studies of already registered (generic) drugs.
6. Approval of Clinical Prescribing Information, e.g. indications, dose; similar to the SmPC (Summary of Product Characteristics) and PIL (Patient Information Leaflet).
7. Establishment of Finished Pharmaceutical Product Specifications through equipment qualification, method transfer, system suitability, and analytical method validation.
8. Qualification of source of materials, e.g. Actives and Inactives.
9. Use of approved/authentic primary and secondary references in analytical techniques.
10. Authorization/Approvals of the marketing literature, e.g. sales persons, detailing material.
11. Description of activities related to Adverse Drug Event monitoring/Pharmacovigilance.
12. The continuous review of marketing authorizations of already registered medicines in terms of their safety and efficacy data obtained from different regulatory agencies.

the technical requirements outlined in Box 1 are a potential way to improve the quality of medicines in Pakistan.

Currently, medicines being registered in Pakistan are not undergoing full evaluation of their safety and quality, especially in terms of their APIs [5]. Some of the suggested requirements, see Box 1, are not currently a mandatory part of the registration of medicines in Pakistan, e.g. the bioequivalence of generic medicines and even submission of the SmPC (Summary of Product Characteristics) and PIL (Patient Information Leaflet). Others, which are covered under the current rules and procedures, are also not being completely fulfilled, such as performing stability studies and validation studies. Ethically and legally, applicants should be bound to fulfill these commitments and thus perform these studies before marketing their medicines. However, in reality very few companies are complying with these commitments and performing such studies before marketing their medicines (S Hussein personal communication). There was a recent incidence of counterfeit medicines at the Punjab Institute of Cardiology which is thought to be a direct result of such deficiencies in the registration process and negligence in following cGMP [31, 32].

Despite these concerns, pharmaceutical manufacturers in Pakistan currently appear reluctant to perform additional tests or provide more comprehensive information about their medicines, during and after registration. This is thought to be due to the potential negative impact this could have on business (S Hussein, personal communication). In fact, the reverse may be true which would lead to improvement in the quality of generics for consumption in Pakistan, and a greater potential for export to other countries.

Recommendations

Here we outline a number of recommendations that should be considered by the Pharmaceutical Evaluation and Registration (PE & R) Division within DRAP, in consultation with Pakistani pharmaceutical companies, to improve the quality of generics produced by domestic manufacturers for use in Pakistan as well as for exportation.

These include a stepwise plan for the implementation of CTDs and new requirements in line with ICH standards, over one to three years, for example:

- Step 1: For new drugs, imported drugs and narcotic and psychotropic drugs. (Two to six months).
- Step 2: For biological (other than imported) and anticancer drugs. (Two to six months).
- Step 3: For anti-tuberculosis (TB), anti-human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDs) and antimalarial drugs (other than) and anticancer drugs. (Two to six months).
- Step 4: For all antibiotics. (Two to six months).
- Step 5: For all essential drugs (except over-the-counter [OTC]). (Two to six months).
- Step 6: For cardiovascular and anti-diabetes drug. (Two to six months).
- Step 7: For all remaining drugs. (Two to six months).

Alternatively:

- In the first phase, requirements already set out by the current rules and regulations should be implemented. This requires no additional effort by the manufacturers to carry out stability studies of API and Drug master files (open part) of the APIs and submission of the established SmPC and PIL of the product. This phase may take three to six months.
- In the second phase, there should be implementation of pertinent technical requirements which are not currently covered under the existing rules and regulations, such as bioequivalence studies. This will require more time as changes or improvements must be made to the infrastructure of DRAP.

Recently, the efforts of DRAP, in collaboration with USP and WHO, to develop the 'Road Map for Strengthening the Registration System of Pharmaceutical Products and Biologicals for Human/Veterinary Use in Pakistan', demonstrates a noticeable step towards improving the quality of medicines in Pakistan. We will be monitoring its progress and making additional recommendations if necessary.

Together with this, there is the ongoing process that seeks to convince pharmaceutical companies through discussions, seminars, and dialogue, of the need to adopt these new requirements for drug registration, to improve patient care and the potential for drug exports. The experiences of other countries that have started to accept such registration dossiers on CTD or e-CTD (Electronic Common Technical Document), should also be communicated within Pakistan to enhance acceptance of updated requirements. These countries include: Australia, Canada, China, Croatia, Japan, Saudi Arabia, Singapore, South Africa, Switzerland, the US, and all EU Member States [33]. In addition, comparison with the pharmaceutical manufacturing industry in Jordan whose population is only eight million compared with 201 million in Pakistan. Jordan currently has 16

pharmaceutical units compared with over 600 units in Pakistan [26, 34]. However, their exports are high with over 80% of produced medicines currently being exported over 60 countries [34, 35]. This includes more than US\$4.5 billion alone to Saudi Arabia [35]. In contrast, Pakistani manufacturers in 2013 only exported US\$1 billion due to concerns with poor quality [25, 36].

The implementation of ICH Standards should also be applicable to already registered medicines. These improvements may be achieved in the same stepwise manner as described above at the time of their application for renewal of registration starting over the coming year.

Other recommendations may include:

- Improved tracking of agreed implementation issues, maintained through dialogue sessions with pertinent pharmaceutical companies under political and governmental control, with the help of external organizations, such as WHO. This should help speed up the adoption of new processes to improve the quality of generics in Pakistan.
- During the transition period and prior to mandatory implementation, voluntary compliance with agreed new data requirements is advocated. Collection of BE (bioequivalence) data, should also be encouraged. This could be achieved through faster approval times and other beneficial regulatory aspects.
- Preparation of a minimum checklist, providing guidance to manufacturers on specific documentation requirements to reduce impurities and improve the quality of API raw materials. Internal staff within the regulatory agencies in Pakistan should familiarize themselves with, and gain an in-depth knowledge of the revised/new requirements. This can be done through attending internal and external training programmes and sharing information amongst peers.
- Providing manufacturers with additional motivation to hasten or oblige the adoption of these new requirements. This could include shorter approval times for pending applications/post-registration variations.

Manufacturers and DRAP may consider the following technical aspects whilst undergoing prequalification of API sources:

- Assessment of API dossier
- Inspection of manufacturing sites
- Random sampling and testing
- Details about handling of complaints and recalls
- Periodic or continuous checks to maintain the prequalification status
- Requirements for assessment of quality from DMF (Drug Master File) or APIMF (Active Pharmaceutical Ingredient Master File), together with the open part and closed part details.

If these measures are adopted, patients can expect good quality generics in the future. This is important, given the extent to which medicines in Pakistan are self-pay. Without such measures, patient care using generics and trust in the healthcare system will continue to be compromised, and there will be increased potential for adverse drug reactions [37]. Successful steps have already been taken to address concerns over counterfeit medicines in Pakistan, which need to continue [38]. The above considerations should be the next step to further improve the availability of safe, effective and affordable medicines in

Pakistan. This is of great importance given the increasing prevalence of chronic illnesses and diseases in this country, where every third person over the age of 40 is vulnerable to a wide range of diseases [39], and 70% of the population lives on less than US\$2 per day [40].

Conclusion

The results of this study document the concerns over the current regulations for assessment of the quality of drug raw materials (APIs) in Pakistan. These need to be urgently addressed to ensure good quality generics in Pakistan for patients, and to improve potential export opportunities. The adoption of WHO and ICH recommended CTD format and WHO prequalification guidelines, to improve the process of registration of medicines in Pakistan, should help improve the current system for registering medicines. Thus, this will enhance the availability of safe, effective and cost-effective generics for patients in Pakistan and other regions. This is starting to happen and will be monitored.

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