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Exploring perceptions of regulators regarding factors affecting quality of nutraceuticals and cosmeceuticals: A qualitative study from Pakistan

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Abstract---Inadequate rules and regulations regarding manufacturing and quality assurance of nutraceuticals and cosmeceuticals are a threat towards safety, quality and efficacy of such products. The aim of the study was to explore the perception of regulatory stakeholders regarding current status, challenges, barriers and solutions for assuring rational use, quality, safety and efficacy of nutraceuticals and cosmeceuticals in Pakistan. A qualitative study design was used. Perceptions of stakeholders were explored using semi structured interview guide by using snowball sampling technique. After data collection, recorded interviews were transcribed verbatim. Transcribed interviews were then subjected to thematic analysis and were analysed for relevant contents. The result of the study highlighted that regulatory guideline for nutraceuticals were available and being followed. Although the policies were available, but strict

implementation of policies is required. The results of the present study concluded that nutraceuticals and cosmeceuticals are of great focus and concern for all the regulatory stakeholders. Majority of the respondents agreed that this is the era of nutraceuticals and cosmeceuticals but unfortunately these are most neglected topic in terms of research and knowledge. Despite of the challenges and barriers faced by regulators related to safe and efficacious use of nutraceuticals and cosmeceuticals, they had constructive and practical ideas about how to embrace the current nutraceutical and cosmeceutical landscape and use the opportunity to develop professional roles that facilitates the appropriate and safe use of nutraceuticals and cosmeceuticals in Pakistan.

Keywords---perceptions, nutraceuticals, cosmeceuticals, qualitative, regulators, Pakistan.

Introduction

During the past few years, the global demand of nutraceuticals and cosmeceuticals has risen as this segment has replaced the conventional medicines and beauty care products used for prevention and management of various clinical conditions [1, 2]. The use and demand of nutraceuticals and cosmeceuticals has drastically hiked in last decade in developed as well as developing countries despite the lack of evidence based clinical data, quality and efficacy concerns and false label claims [2, 3]. The use of nutraceuticals is highly prevalent in specific diseases involving nutritional deficiencies and various age groups especially elderly [4]. Similarly, cosmeceuticals are being considered as the future of skin care. The cosmeceutical industry is evolving, and highly advanced skincare solutions are now available in the market which have replaced the traditional skincare treatments. Cosmeceuticals are being considered as a cosmetic-pharmaceutical hybrids intended to enhance the health and beauty of skin by dermatologists worldwide (Wanjari and Waghmare, 2015). However, nutraceuticals and cosmeceuticals both fall into a gray zone due to lack of information on their clinical efficacy, safety and quality, unproven therapeutic effects and misleading label claims [5].

Nutraceuticals are widely used in various health conditions in by consumers as the use of dietary supplements in developed countries varied between 30 and 90% [2]. A study conducted in India showed that more than 90% of population uses dietary supplement for various health conditions [6]. Large scale surveys have revealed an increasing popularity of complementary and alternative medicine use in North America, Australia and Europe in recent decades [2]. A study conducted in Pakistan highlighted that 59.3% of the consumers visiting pharmacies purchased nutraceuticals [7]. It has been observed that the use of alternative and dietary supplements is common in the country due to misinformation on allopathic medicines regarding its therapeutic efficacy and side effects [8]. As cosmeceuticals is considered as fastest growing segment in skin care and beauty industry, its global demand is increasing day by day [9]. A study conducted in US

stated that there are over 400 suppliers and manufacturers of cosmeceutical products and an estimated growth of 7.4% has been seen annually [10].

As manufacturers are not required to submit clinical efficacy and safety data for their products to the FDA before obtaining marketing approval, the lack of this information presents a significant health risk to the public that reflects a need to make regulatory guidelines strict so that product marketed must be safe to use [11]. A study suggested that increasing regulatory requirements by regulators complicate the design, testing, and marketing of these substances [12]. A study concluded that there are an increasing number of nutraceutical supplements emerging in a variety of distribution channels, especially in the internet-based sales. At the same time, safety concerns of the governmental authorities lag behind the marketing strategies of distributors. There are multiple brands available in the market with little scientific evidence of efficacy, no clear proof of ingredients, no control of their shelf life and no knowledge of side effects or supplement-drug interactions [13]. A study concluded that it is necessary to clearly define the rules and laws for nutraceuticals for regulating their production and distribution, showing their real efficacy and safety carrying out more in vitro and in vivo studies [5]. Another study concluded that the present accumulated knowledge about nutraceuticals represents undoubtedly a great challenge for nutritionists, physicians, food technologists and food chemists so it is important to address pharmaceutical and clinical issues by further research [4]. Research conducted in South Australia mentioned that most CAMs are “Listed” (L classification) on the Australian Register of Therapeutic Goods (their stated contents and safe manufacture have been accepted without audit and without proof of efficacy) and can be sold and advertised with “low level” claims. In contrast, “Registered” (R classification) medicines have been assessed for quality, safety and efficacy, so there must be some regulatory guidelines to ensure the safety and efficacy before marketing these products [14]. A study conducted in USA revealed that laws were passed to ensure the safety of new dietary ingredients introduced into the United States marketplace. But more than 11 years later, these laws are frequently misunderstood, and more frequently ignored [15]. The rules and regulations for Alternative Medicines and Health Products are available in Pakistan however the implementation is poor. A study conducted in Pakistan investigated high concentration of heavy metals in cosmetic products that can be a threat to human body. That reflects the need for proper regulations and good manufacturing practices in Pakistan [16]. Inadequate rules and regulations regarding manufacturing and quality assurance of cosmeceuticals are also a threat towards safety, quality and efficacy of such products. Therefore, the present study was designed to explore the perception of regulatory stakeholders regarding current status, challenges, barriers and solutions for assuring rational use, quality, safety and efficacy of nutraceuticals and cosmeceuticals in Pakistan.

Methodology

Study Design

A qualitative study design was used to explore perception of regulators regarding factors affecting quality and safety of nutraceuticals and cosmeceuticals in Pakistan.

Ethical Approval

Study approval was taken from Ethical Committee of Hamdard University. Informed consent for participation was taken from respondents participating in the research. Confidentiality agreements were signed by respondents to ensure that their personal information will not be disclosed, and all the information taken from participants will solely be used for research purpose and will not be misused.

Study Site and Respondents

Study site for this research was Drug Regulatory Authority of Pakistan (DRAP). Study respondents were regulatory officers appointed at DRAP.

Sampling Technique

Nonprobability sampling technique was used i.e. Snow ball sampling was adopted as it is the best way of identifying the respondents having common characteristics, experience and job profile which were difficult to contact. In snowball researcher initially identified the first respondent and then he was requested to suggest more from his contacts that were included in our research. Interviews were conducted till saturation point was achieved.

Data Collection Tool

Data was collected using a semi-structured interview guide. Interview guide was composed of close-ended and open-ended questions to get a better insight of exact situation and also a detailed view from Respondents. Interview guide had different sections focusing on different issues regarding quality and safety of nutraceuticals and cosmeceuticals. First section had questions regarding the current status of nutraceuticals and cosmeceuticals in the country. Second section had questions regarding factors affecting safety and quality and third section had questions regarding the challenges and barriers faced and solutions for them. Pilot testing was conducted on 10% of the total sample to check the reliability of the data.

Data Collection Procedure

Interviews were recorded after getting consent from the respondents. When necessary, probing questions were used. Estimated interview time was 20-30 minutes. Every respondent was provided with equal opportunities and time to fully express his views. All the recorded interviews were transcribed verbatim. Transcribed interviews were then subjected to thematic analysis and were analysed for relevant content.

Results**Demographic Characteristics**

Out of total respondents, 14.3% (n=1) were currently working in Registration department while 85.7% (n=6) were working in Health & OTC department of Drug Regulatory Authority of Pakistan (DRAP). Only one female respondent was working in health & OTC department. Regarding the experience of respondents related to Health & OTC department, 57.1% (n=4) had work experience of 1-4

years while 42.9% (n=3) had work experience of more the 5 years. A detailed description is given (Table 1).

Table 1 Demographic Characteristics

Code	Gender	Qualification	Experience	Current Designation	Department
Regt 01	Male	M.Phil	7 years	Assistant Director	Health & OTC
Regt 02	Male	Pharm.D	4 years	Assistant Director	Health & OTC
Regt 03	Male	Pharm.D	1 years	Assistant Director	Health & OTC
Regt 04	Male	M.Phil.	7 years	Assistant Director	Health & OTC
Regt 05	Male	Pharm.D	2 years	Assistant Director	Health & OTC
Regt 06	Female	Pharm.D	4 years	Assistant Director	Health & OTC
Regt 07	Male	M.Phil.	6 years	Assistant Director	Registration

Regt: Regulator

Theme 1: Role of DRAP in Governance of Quality of Nutraceuticals and Cosmeceuticals in Pakistan

Most of the regulators indicated that Drug Regulatory Authority of Pakistan has devised Rules for Nutraceuticals commonly known as SRO/412 for governing the quality of Nutraceuticals in Pakistan. Moreover, they highlighted that as far as Cosmeceuticals are concerned; they are not enlisted or regulated in Pakistan under any act or rule till date. However, DRAP is trying to devising some rules and regulation for cosmeceuticals as well to ensure that quality products can be manufactured and prompted.

'DRAP ensures quality of nutraceuticals through implementation of SRO/412. Only those products can be manufactured which are enlisted through DRAP according to all the rules given in SRO/412. We ensure that good manufacturing practices are being followed through GMP inspections and then issue GMP certificate for 1 year. We verify that GMP's must be followed before, during and after manufacturing during these inspections' (Regt 01).

'DRAP has devised rules for nutraceuticals known as SRO/412. All the nutraceutical manufacturing units must be approved by DRAP and they must have Form-6 on which all the sections must be clearly mentioned. They can only manufacture and sale those nutraceuticals which are enlisted by DRAP. As far as cosmeceuticals are concerned, currently there are no rules for them, but obviously there will be in future' (Regt 02).

'DRAP confirm that nutraceuticals are medicines that must be manufactured in a hygienic manufacturing unit similarly as other pharmaceutical medicines are prepared. Moreover, they must be enlisted to make sure that no toxic ingredient or quantity has been used in formulation. Cosmeceuticals are currently not in our domain, as we follow SRO/412 and there is no word like cosmeceuticals in it' (Regt 03).

'DRAP is constantly working to improve the quality of Nutraceuticals, as these are the OTC medicines most frequently used these days. We are trying to play our role to make sure that quality products are manufactured and marketed. We follow a stepwise process to confirm quality. We approve appropriate layout, then inspect the manufacturing unit, issue Form-6, enlist the products after detail study of all the necessary documents and only allow those products to be manufactured and sold which are qualify for enlisting' (Regt 07).

Theme 2: National Policies and Guidelines for Regulating Nutraceuticals and Cosmeceuticals

(a) Availability of Guidelines for Nutraceuticals and Cosmeceuticals

Almost all of the regulators stated that they do have generalized rules & regulations for nutraceuticals which are being followed in routine practice. However, some of the regulators mentioned that these guidelines are not concrete as some of the important aspects are missing which raise ambiguities and confusions among people. All the regulators highlighted that there are no guidelines available for ensuring product safety of cosmeceuticals.

'SRO/412 gives clear and complete guidelines regarding nutraceuticals, starting from its definition till its sales. As far as cosmeceuticals are concerned, SRO/412 do not have any such term like Cosmeceuticals, so there are no rules on cosmeceuticals devised yet' (Regt 01).

'DRAP provides concrete guidelines but there is always room for improvement. SRO/412 has almost every important policy that is required for manufacturer as well as for products. But cosmeceuticals are not regulated or enlisted under any guideline yet. There is an urgent need to devise some guidelines as they have some active ingredient meant to be used on skin so they must be regulated to ensure safety of these products' (Regt 04).

'DRAP has all the basic guidelines for nutraceuticals clearly mentioned in SRO/412, but there are few things that are not clear or that might be ambiguous for some people, regarding these different notifications are released time to time' (Regt 02).

'We do have guidelines for Nutraceuticals however few deficiencies exist in the policies. We need to improve and update these policies addressing the deficiencies however these policies provide all the basic information. But we don't have any guidelines to regulate cosmeceuticals yet' (Regt 07).

(b) Updation and Revision of Guidelines

Different opinions of regulators were observed regarding updation and revision of policies or guidelines of Nutraceuticals. Some of them were of the view that policies should be updated on annual basis while some believed that they must be revised bi-annually. On the other hand, some suggested that they must be updated throughout the year whenever there are some obvious changes in the rules or revised whenever required.

'In my opinion, all the guidelines must be revised annually, as there are lot of additions and subtractions that we have to do according to the changes' (Regt 03).

'These guidelines must be revised bi-annually, as there are lot of new changes and clarifications in different aspects which must be the part of these guidelines' (Regt 02).

'I personally believe that these guidelines must be revised throughout the year according to necessary requirements' (Regt 01).

'They must be revised when required, due to an obvious change in the rules' (Regt 05).

(c) Mechanism for Implementation of Guidelines

Almost all the regulators believed that frequent and one-one interaction with manufacturers could be very beneficial for implementation of policies as manufacturers are the main key stake holders for adopting policies provided by DRAP and for manufacturing of quality and safe product.

'The interactive sessions between manufacturer and regulators must be organized for better understanding and implementation of policies. These interactions will lead to two-way interactions, so we can understand their problems and give a better solution to them' (Regt 01).

'In my opinion, one of the effective ways for implementation of policies is maintaining good relationship with manufacturer. One on one discussion can provide a platform for developing better understanding between stake holders and regulators. But it is very difficult to arrange such interactions as there are lots of manufacturers. We can take a step starting from south to north by targeting group of manufacturers, but it's no doubt a very complex procedure. However, we are now trying to interact through social media by making videos showing softer image of DRAP and help in better understanding of policies' (Regt 05).

'Frequent interaction between manufacturer and regulators can help in implementation of policies in a better way, as they will come and communicate with us which will develop a better relation. In this way, they can also interact with us and discuss problems faced at their side in implementing policies and in turn we can provide solutions' (Regt 04).

'The interaction between manufacturer and regulator will help in implementation of new techniques/ methods. A close interaction will help in training of personnel and also easy understanding of policies' (Regt 03).

(d) Barriers Faced in Implementation of Policies

Most of the regulators mentioned that they are unable to implement policies regarding nutraceuticals in its actual context due to the reluctant behavior of manufacturers. Lot of cases have been filed by manufacturers against DRAP and SRO/412, as they are not willing to accept SRO/412. While one of the regulators mentioned that no hurdle is faced in implementation of policies regarding nutraceuticals.

'One of the main hurdles faced by DRAP is the reluctant behavior of manufacturers they are not willing to accept SRO/412 till now, which makes it difficult for us to implement the policies in a better way' (Regt 01).

'The biggest hurdle is that manufacturers don't accept SRO/412. They have filed so many cases in High Court against SRO 412 and DRAP. The main cases CP-D487/2014 filed in Sindh High court, Karachi whose main stance was that SRO/412 must not be implemented, nutraceuticals must not be regulated as regulation of nutraceutical is not DRAP'S Domain, and it is violation of business law. Another case was 3973/2017 filed in Lahore High Court in which Dawakhana hakeem ajmal clubbed with 100 + industries filed a case against DRAP, their main stance was DRAP act is not appropriate as it is the violation of freedom of business act article-18. Therefore, it must not be implemented so that they can do their business freely without any regulation. In 2020, finally both these cases were resolved and high court states that SRO/412 and DRAP act is valid and must be implemented and the stance was wrong' (Regt 04).

Theme 3: Operational Framework for Enlistment of Nutraceuticals and Cosmeceuticals

(a) Required Information for Enlistment of Nutraceuticals

All the regulators mentioned that Form 3 is designed specifically for enlistment of local nutraceuticals. All the requirements are clearly mentioned in it. Moreover, a checklist is also provided to all the manufacturers for their ease and understanding.

'We require recommended formulation dose, evidence master formula, manufacturing & testing methods, monographs, stability data, storage conditions, packaging and product information along with appropriate fee for enlistment' (Regt 06).

'DRAP requires company enlistment certificate and formulation of the product basically, along with all the requirements given in Form-3 or on provided checklist' (Regt 01).

'All the basic requirements mentioned in Form-3 for local products and form 5 for import products, including formulation design, product information regarding storage, packaging & testing methods and reference of formulation' (Regt 02).

(b) Quality and Content of Information to Deliver Quality Products

Half of the regulators believed that as nutraceuticals are enlisted and not registered in Pakistan, so the required information provided by manufacturer is sufficient to enlist the product and if this is manufactured by adopting Good manufacturing practices then it will be safe to use and of good quality. However, the other half believed that the quality of nutraceuticals cannot be just ensured through the documentation, so it is necessary to perform stability, safety and toxicological studies as well as qualitative and quantitative assay before applying for enlistment to DRAP to ensure the safety and efficacy.

'On our side, this required information is enough basically we deal with nutraceuticals and their enlistment through documentations, so we have enough documents to state that a product manufactured according to the guidelines is of good quality' (Regt 02).

'In my opinion the information given in the required documents is enough as nutraceutical is over-the-counter product and enlisted in Pakistan not registered, so we are basically concerned with the enlistment of product in documented form. We will just approve the product that has complete documents and formulation is acceptable, maintaining quality of the product is manufacturer's duty' (Regt 04).

'Basically, we are just dealing with enlistment of product, we are only concerned with the safety of the formulation. We are not responsible for manufacturing of that product, so I can say if enlisted formulation is manufactured according to GMP only, then it will be a quality product' (Regt 05).

'Personally, I don't think so that this information is enough to make a quality product, I believe that quality can be maintained, only if sample batch is prepared by manufacturer and then sent to DTL after all the tests, it should be applied in DRAP with all paper work for enlistment, along with report from DTL' (Regt 01).

'My opinion might be different but I believe that information is not sufficient for delivering quality products to the consumer. If we want to deliver quality products then there must be involvement of all the departments of health, that ensure that raw material is up to mark, manufacturing has followed GMP guidelines, testing laboratories must performed quantitative and qualitative tests, stability studies must be performed along with safety and toxicological studies only then we can make sure that quality product is used by consumer' (Regt 07).

(c) Availability of Rules for Pricing

All the regulators confirmed the unavailability of Rules for pricing of Nutraceuticals. Mostly prices for nutraceuticals are set by the manufacturer through market analysis. Moreover, regulators mentioned that DRAP is working on devising Rules for pricing of nutraceuticals. Some of the regulators were of the view that implementation of pricing rules will be a difficult task to accomplish as manufacturers are gaining huge profit from nutraceuticals. Moreover, nutraceuticals fall in health supplement category, so it will be difficult to control prices.

'There are no rules for pricing of nutraceuticals given by DRAP, manufacturers can set price at their own, no matter how expensive it is, but pricing department is working on it, which will be implemented soon' (Regt 03).

'There are no rules for pricing of nutraceuticals yet. Although DRAP is working for devising pricing rules for nutraceuticals but it will create a great hype among manufacturers as they are getting huge profit from these nutraceuticals' (Regt 07).

'No rules on pricing of nutraceuticals have been devised yet by DRAP. But DRAP is working on designing a policy for pricing of nutraceuticals but all over the world there are rules and regulation for prices of essential drugs only, and nutraceutical are health supplements and in my opinion, we cannot control the prices of nutraceuticals' (Regt 01).

'There are no rules to set a price for nutraceuticals yet. The main reason of its unavailability is that pricing department that deals with designing and implementation of pricing rules, has only word 'Therapeutic Goods' in it, but Nutraceuticals don't fall under therapeutic goods, so they haven't designed any policy yet, but they are working on it' (Regt 04).

(d) Authenticity of Labelled Claims

Almost all the regulators confirmed that the authenticity of claims mentioned on label of nutraceuticals are verified. Any false or exaggerated claim is not allowed under labeling rules for nutraceuticals. Also, if there is any ingredient in the formulation that doesn't seem in accordance with the recommended use then the clarification from manufacturer is requested. Some of the regulators also mentioned that recent research papers and books are consulted to make sure that all the ingredients in the product are actually meant for its use.

'In general, we know that which ingredient is used for what purpose as we have all the evidence-based studies for these ingredients. If we find any doubtful ingredient that is not in accordance with use, then we ask for clarification of that specific ingredient in the formulation, in order to make sure

that the ingredients used in it gives that desired effect as mentioned on the label' (Regt 05).

'DRAP is ensuring that any exaggerated or false claim must not be written on the label, as these are over-the-counter products and health aids, so should only have generalized recommended uses similarly proved by different researches e.g., calcium and vitamin D for better bone health, fennel and chamomile for colic, etc.' (Regt 07).

'Nutraceuticals are over-the counter products so we cannot use exaggerated claims on it. So, we ensure that general use must be mentioned on it that is known to everyone and proper research data is available for them' (Regt 04).

(e) Guidelines for Local Manufacturing, Import and Export of Cosmeceuticals

There are no guidelines or policies available for manufacturing, import and export of cosmeceuticals. Regulators highlighted that cosmeceuticals falls in the grey zone, as they are neither drugs nor cosmetics. It has become the most debated section because of its rapidly growing market. There is need to devise guidelines for cosmeceuticals as early as possible. As in Pakistan, toxic and harmful substances were found in different medicated cosmetics, which can damage skin.

'Cosmeceuticals is the most debated section. There are more debates and discussions but fewer outcomes. There is a conflict between MDMC and Health & OTC departments of DRAP, one says it's your domain and vice versa. So, there are no rules of manufacturing, import and export of cosmeceuticals yet, but there will be proper rules in near future' (Regt 05).

'There are no rules given by DRAP on cosmeceuticals. They are working on it since long time because of its increasing demand and usage. And we badly need these cosmeceutical rules as there is a large use of toxic and harmful substances in medicated cosmetics' (Regt 07).

'We all know that the cosmeceuticals fall in grey zone. We ourselves are not clear regarding policies on cosmeceuticals, as these are neither cosmetics nor drugs, it is an incorporation of both. As we know that cosmeceutical market is growing rapidly, so some guidelines must be available to regulate the local manufacturing, import and export. Now-a-days cosmeceuticals are imported and exported according to Import and Export rules for all goods (Regt 02).

(f) Influence of legal policies

All the regulators had same opinion that legal policies leave a positive influence in improving the quality of nutraceuticals. Regulators mentioned that manufacturing practices were remarkably improved. Manufactures are trying to implement GMP's in order to manufacture a quality nutraceutical. Most of the regulators mentioned that they have seen lot of improvement in manufacturing units as well as in quality of nutraceuticals.

'Under the influence of these legal policies quality of nutraceuticals are maintained by adopting Good manufacturing practices' (Regt 02).

'After implementation of SRO/412, manufacturing standards have been increased; people are not manufacturing nutraceuticals in small rooms in unhygienic conditions. But now we make sure that manufacturing facility must complies standards, which ultimately improves the standard of product

manufactured. Even in terms and conditions mentioned on Form-7 it is clearly mentioned to maintain quality of product is manufacturer responsibility' (Regt 04)

'After implementation of SRO/412, we can see visible change in quality of products' (Regt 07).

'We have seen lot of improvement in nutraceutical manufacturing units as well as in quality of nutraceutical products after implementation of SRO/412' (Regt 03).

(g) Legal Actions against Non-compliance with Policies

Regulators highlighted that in case of non-compliance with the policies for manufacturing and sales of nutraceuticals legal action are taken by DRAP. These actions include fine, imprisonment, cancellation of enlistment certificate of product or even manufacturing unit. All these legal actions adopted are clearly mentioned in Rule 11 of SRO/412 and in DRAP Act, 2012.

'Rule 11 of SRO/412 has all the actions that must be taken if any violation of rules or policy occurs' (Regt 04).

'There are lot of cases in which nutraceutical manufacturers are manufacturing nutraceuticals drugs not enlisted by DRAP, or spurious or sub-standard drugs. These doubtful products are picked up by Drug inspectors, sent to Drug Testing Laboratory for quantitative and qualitative assays and case is filed against them along with laboratory evidences' (Regt 07).

'Legal actions including fine, imprisonment and cancellation of manufacturer's license must be taken in case of violation of rules' (Regt 01).

Theme 4: Role of Pharmacist in Promoting Safe Use of Nutraceuticals and Cosmeceuticals in Pakistan

Various roles that can be performed by pharmacists were mentioned by all of the regulators for promoting safe and efficacious use of nutraceuticals and cosmeceuticals. Pharmacist working in every domain can play its own role and ultimate goal is to provide safe nutraceutical and cosmeceuticals to the end user. Pharmacists working in regulatory department must ensure that formulation designed by manufacturer must not have any toxic effect and must be stable. Pharmacists working in manufacturing units have most important role starting from ordering raw materials from well-reputed vendors, maintaining manufacturing standards, assuring quality of the product at every step of manufacturing. Pharmacist working in R & D department can identify toxic materials, specify limits of daily use, can develop testing method of finished product as well as raw material whose monographs are not available in pharmacopoeia. Pharmacists working in marketing department must only market and promote sales of those nutraceutical and cosmeceuticals proven by evidence-based data. Community and Hospital pharmacists can help the buyer in selection of better nutraceutical and cosmeceuticals and also can counsel the consumer regarding its use, interactions, side effects and toxicity. Pharmacist working in academia can add chapters related to cosmeceuticals and nutraceuticals, so that the pharmacy students can improve the knowledge regarding this subject.

'Pharmacist has main and most important role starting from raw material purchase till sale of product. As pharmacist is dealing with everything, he is responsible for quality of raw material. He is the main expert during manufacturing of the product its testing, packing, then it is sold at different pharmacies, there community pharmacist must counsel the patient regarding nutraceuticals' (Regt 01)

'Pharmacists are playing a great role in different departments like pharmacist of R & D department are creating rational formulations of different dosage forms, QC pharmacist are developing new specific testing methods of finished products that are not available in pharmacopoeias and pharmacist working in DRAP are identify presence of any toxic and poisonous materials like mercury/selenium sulfide, etc.' (Regt 03).

'Pharmacist has main role in promoting safe use of nutraceuticals. Those involved in manufacturing must ensure that the raw materials they purchase from venders is of good quality and all the vitamins mentioned in the formulation are added in their exact quantities. Secondly, as nutraceutical is not a prescription item, so community pharmacist can help consumer at the time of dispensing in selection of better nutraceutical and counseling regarding its use. Then pharmacist working in marketing can play role by marketing their product according to its actual use not by false claims. While pharmacist working in regulatory department can make sure that all the required documents necessary for maintaining the quality of nutraceuticals have been submitted' (Regt 04).

Theme 5: Challenges and Barriers in Promoting Safe and Efficacious use of Nutraceuticals and Cosmeceuticals

(a) Lack of Training of Pharmacist

barriers, the foremost is of pharmacist knowledge and training as he/she is responsible for delivering nutraceutical or cosmeceuticals to the end user.

'I guess the main challenge is at part of pharmacist especially hospital and community pharmacist. They are not trained enough to counsel the consumer regarding its safe use. Mostly consumers are using them un-necessary and our pharmacist is capable enough to convince end user not to use them un-necessarily. We cannot stop prescribers from writing it but pharmacist can play their role while dispensing' (Regt 01)

(b) Lack of Awareness among General Public

Some of the regulators mentioned that one of the most important barriers in delivering safe and efficacious use is limited knowledge of general public or consumers. They are un-aware that these nutraceuticals and cosmeceuticals might cause harm when used in excessive amount or un-necessarily. They are using them because either it was prescribed by their physician or are compelled to purchase them through some advertisement without knowing that it may cause toxicity.

'I guess one of the main challenges is lack of awareness among public, as they take these nutraceuticals not for any specific condition and consider it a magic pill. Sometimes they use it un necessarily in large doses that might be harmful for them' (Regt 06).

'The main challenge in my opinion is lack of knowledge on user as well as on pharmacist end. Users don't know about nutraceuticals they just use it on doctor's prescription or on someone's recommendation. Pharmacists don't know about these nutraceuticals too. There are lots of nutraceutical advertisements on social media that is leading towards un-necessary and over consumption of nutraceuticals' (Regt 07).

(c) Unavailability of Guidelines for Cosmeceuticals

Some regulators believed that the most important challenge in promoting safe use of cosmeceuticals is lack of polices for manufacturing of cosmeceuticals. Only under specific guidelines the manufacturing of cosmeceuticals and safe use could be promoted.

*'One of the challenges in promoting safe use of cosmeceuticals is lack of policies regarding cosmeceuticals, toxic and harmful substances are used in them including heavy metals that might damage skin badly' (Regt 03).
'Cosmeceuticals is an important domain and need of this era and its growing market reflect the need of guidelines or policies for manufacturing cosmeceuticals' (Regt 04).*

(d) Lack of Implementation of Manufacturing Standards

Few regulators were of the view that complete implementation of manufacturing standards is one of the main challenges in promoting safe and efficacious use of nutraceuticals. As they believed that we can be only sure about the quality of nutraceuticals only if they are manufactured in a hygienic manufacturing unit that adopts Good Manufacturing Practices and purchase raw materials both active and inactive from vendors who provide up-to-mark quality material.

*'There are lot of barriers in promoting safe and efficacious use of nutraceuticals, but one of the main in that nutraceutical manufacturer are not completely following SRO/412 and GMP guidelines which lead to sub-standard nutraceuticals that might be harmful for the end user' (Regt 02).
'Manufacturing units are not following GMP guidelines that must be followed for manufacturing good quality products. Quality of raw material is not good, as manufacturer purchase raw material from vendors who give them at lower prices regardless of their quality and tests of these raw materials are also not performed' (Regt 04).*

(e) Lack of Evidence Based Data

Evidence based data and research literatures lack regarding nutraceuticals and cosmeceuticals as described by most of the regulators to be one of the barriers.

*'As worldwide nutraceuticals and cosmeceuticals are over the counter products so main challenge is that there is no authentic clinical data available for new formulations to justify their use' (Regt 03).
'There is a lack of literature on nutraceuticals and cosmeceuticals. There are no evidence-based studies that can confirm the use, side effects and toxicity of nutraceuticals or cosmeceuticals' (Regt 07).*

(f) Lack of Work Force in DRAP

Limited number of staffs is working in Health & OTC department was also seen as big challenge for governing a huge number of nutraceutical manufacturing units working in Pakistan, so it's difficult to maintain quality of nutraceuticals.

'Due to limited workforce, work burden is immense. There are 1200 plus Nutraceutical and lot of products units enlisted by DRAP. It's becoming difficult to work efficiently with this limited workforce' (Regt 05).

Theme 6: Strategies for Promoting Safe and Efficacious use of Nutraceuticals and Cosmeceuticals**(a) Active Role of Manufacturer for Policy development and implementation**

Among multiple strategies suggested by regulators one of them was the involvement of manufacturers in development and implementation of policies. As manufacturers are the key stake holders, so they can actively play their roles in implementation of policies in a better way.

'Manufacturers are the stake holders and can implement and ensure quality manufacturing of nutraceuticals by adopting the policies given by DRAP. Frequent interactive sessions must be organized between regulators and manufacturers as they can discuss the difficulties they face in implementation of policies and can understand the policies in a better way. Regulators can also understand their difficulties and current situation and can develop a policy that is beneficial for both the group for ensuring quality of nutraceuticals and cosmeceuticals' (Regt 03).

'Manufacturers do visit DRAP to discuss issues and in my opinion this interaction must occur frequently as manufacturers can understand better if we discuss verbally with them instead of what is written' (Regt 06).

(b) Training of Pharmacist

Most of the regulators suggested that there is a need to train and educate pharmacist working at community and hospital level, as they are the ones who have close interaction with consumers and can counsel end users in a better way.

'By enhancing knowledge and communication skills of pharmacist, they can counsel the end user in a better way and can minimize all the misconceptions of the consumer regarding nutraceuticals' (Regt 01).

(c) Strict Implementation of Policies

Almost all the regulators highlighted that policies regarding manufacturing and sales of nutraceuticals must be implemented in a strict way, as only then safe and efficacious use of nutraceuticals could be ensured.

'Every nutraceutical manufacturer should follow SRO/412 in true spirit and letter' (Regt 02).

'Frequency of GMP inspections must be increased to ensure that good manufacturing practices are being followed. Vendors must be specific and

approved by DRAP, so that all the manufacturing units purchase raw material that must be of good quality. Proper tests of raw materials and finished product must be performed in order to maintain their quality' (Regt 04).

(d) Promoting Public Awareness

Many regulators recommended that pharmacist must play their active role in counseling of general public in order to promote safe use of nutraceuticals.

'Pharmacist must play their role in promoting awareness among general public, through seminars, discussion or by using social media platform to inform public that they must use nutraceuticals in limited amount under specific health conditions' (Regt 06)

'Public awareness campaigns must be devised regarding safety and use of nutraceuticals' (Regt 07).

(e) Promoting Conduction of Evidence Based Studies at National level

Some regulators proposed that as there is lack of literature and evidence-based studies regarding nutraceuticals. Therefore, Government must conduct clinical studies at national level.

'There must be clinical studies conducted by the government to produce evidence-based data' (Regt 03).

(f) Increase in Work Force

Some regulators proposed to increase staff working in nutraceutical department, so policies could be implemented in a much better way through surprise inspections and auditing.

'Work force might be increased, so that half of them can perform inspections of manufacturing units to ensure quality of nutraceuticals by ensuring implementation of GMP and ultimately delivery of quality products to the public' (Regt 05).

Discussion

The market of nutraceuticals and cosmeceuticals is on the rise as both are widely used for their claimed benefits on the body and skin. However, the presence of a wide variety of local and imported brands in the Pakistani market pose a risk towards health of consumers. There is a need of developing and implementing strict regulations for registration, manufacturing and marketing of such products in the market as over the counter. The current study qualitatively evaluated the perceptions of regulators regarding the factors that affects the quality, efficacy and safety of nutraceuticals and cosmeceuticals available in Pakistan. The result of present study reported that majority of the respondents working in Drug Regulatory Authority of Pakistan reported that DRAP has devised rules for governing the quality of nutraceuticals which are commonly known as SRO/412 and they are being followed in routine practice. However, some of the regulators mentioned that these guidelines are not concrete; some of the important aspects are missing that raises ambiguities and confusions among manufacturers and importers. Majority of the

respondents had different view regarding updation and revision of policies and guidelines for nutraceuticals. Some of them were of the view that policies should be updated on annual basis while some of them stated that they must be revised bi-annually. Some were of the opinion that they must be updated throughout the year whenever there are some obvious changes in the rules. Whereas some respondents stated that it must be revised whenever it is required. Similar findings were reported in a study conducted in USA, which highlighted that dietary supplement health and education act (DSHEA) regulates and make sure that all the nutraceuticals introduced in the market are safe. FDA in near future is planning to remove all the unsafe dietary supplements from market by evolving new laws and regulations [15].

The presence of appropriate legal policies for manufacturing, marketing and sales of nutraceuticals and cosmeceuticals has a positive influence on improving the quality of nutraceuticals. The majority of the respondents working in the regulatory department stated that manufacturing practices were remarkably improved by the implementation of strict regulations. Most of the respondents mentioned that they had seen a lot of improvement in manufacturing units as well as in quality of nutraceuticals. Similar findings were seen in a study conducted in India which highlighted that regulatory department ensures that every manufacturing unit follows the regulatory guidelines and good manufacturing practices [17].

In order to ensure the presence of quality nutraceuticals, it is necessary that policies are devised by inclusion of all key stakeholders involved in the process. The present study highlighted that respondents were of the view that regulators were unable to implement policies regarding nutraceuticals in their exact form because of the reluctant behavior of manufacturers. However, one of the regulators mentioned that they don't face any hurdle in implementation of policies regarding nutraceuticals. Regulators highlighted that if non-adherence against the policies for manufacturing and sales of nutraceuticals was reported then legal action was taken by DRAP. These actions included fine, imprisonment, cancellation of enlistment certificate of product or even manufacturing unit. Almost all the regulators believed that frequent and one to one interaction with manufacturers could be very beneficial for implementation of policies as manufacturers are the main key stake holders for adopting polices provided by DRAP and for manufacturing quality and safe product. Similar findings were reported from a study conducted in USA which reported that manufacturers were of the view that policies regarding nutraceuticals are difficult to adopt but regulatory department stated that despite all the difficulties faced by manufacturing companies, they must adopt legal regulations in order to participate in removing unsafe health supplements from the market [15].

It is necessary to develop clear guidelines and documentation policies regarding registration and enlistment of nutraceuticals to ensure quality. The results of the present study revealed that respondents mentioned that there is Form-3 designed specifically for enlistment of local nutraceuticals. Moreover, there is a checklist provided to all the manufacturers which includes ingredients along with quantities, recommended use, dosage, label, evidence of availability in

market and stability data. Similar findings were reported in a study conducted in USA that highlighted that all the new dietary ingredients files must include name and detail description of ingredients, quantities, dosage including maximum daily consumption, recommended use along with label and evidence of safety data [15]. The study reported that half of the regulators believed that as nutraceuticals are enlisted and not registered in Pakistan, so the required information provided by manufacturer is sufficient to enlist the product and if this is manufactured by adopting good manufacturing practices then it will be safe to use and of good quality. However, half of the regulators believed that the quality of nutraceuticals cannot be ensured just through the documentation, so it is necessary that to perform stability, safety and toxicological studies as well as qualitative and quantitative assay before applying for enlistment in DRAP. Similar findings were reported by a study conducted in Australia that highlighted that alternative medicines are listed in Australian register of therapeutic goods that means they can be manufactured without auditing and proof of efficacy however an expert committee on complementary medicine has recommended changes in regulatory framework to ensure safety and efficacy [14].

The specific health claims on the labels of nutraceuticals need to be monitored to ensure their appropriate use. The current study reported that almost all the respondents working in regulatory department confirmed that they verified the authenticity of claims mentioned on label of nutraceuticals. Some of the regulators also mentioned that they referred to recent research papers and books to make sure that uses of all ingredients were verified. Similar findings were reported by a study conducted in Germany that reported that European Union has made regulations regarding labels that verifies that labeled claims do not include any misleading information for consumers [18]. The current study revealed the unavailability of rules for pricing of nutraceuticals. The respondents highlighted that mostly prices for nutraceuticals are set by manufacturer through market analysis. Moreover, regulators mentioned that DRAP is working on devising Rules for pricing of nutraceuticals. Some of the regulators were of the view that implementation of pricing rules will be a difficult task to accomplish as manufacturers are gaining huge profit from nutraceuticals. Similar findings were reported in a study conducted in India which highlighted that one of the challenges is high prices of nutraceuticals that reflects the need to devise some rules for pricing of nutraceuticals [19].

The use of cosmeceuticals has increased in the past few years in the Pakistani market. This study highlighted that cosmeceuticals are not enlisted or regulated in Pakistan under any act or rule. However, DRAP is making an effort in devising some rules and regulations for manufacturing, import and export of cosmeceuticals so that quality products can be manufactured and prompted. Majority of the respondents highlighted that cosmeceuticals falls in the hazy zone as they are neither classified as drugs nor cosmetics. There is a need to devise guidelines for cosmeceuticals as early as possible. Similar findings were reported in a study conducted in India which revealed that cosmeceuticals must be regulated before marketing in order to confirm their safety, efficacy and labeled claims and to clear doubts among consumers [20].

Pharmacists can play an efficient role in promoting safe and efficacious use of nutraceuticals and cosmeceuticals. The majority of the regulators were of the view that pharmacists working in every domain can play their role in providing safe nutraceutical and cosmeceuticals to the end user. Pharmacists working in regulatory department must ensure that formulation designed by manufacturer must not have any toxic effect and must be stable. Pharmacists working in manufacturing units have the most important role starting from ordering raw materials from well-reputed vendors, maintaining manufacturing standards, assuring quality of the product at every step of manufacturing. Pharmacists working in the R & D department can identify toxic materials, specify limits to be used, can develop testing methods of finished product as well as raw material whose monographs are not available in pharmacopoeia. Pharmacists working in the marketing department must only market and promote sales of those nutraceutical and cosmeceuticals that have evidence-based studies. Community and hospital pharmacists can help the buyer in selection of better nutraceutical and cosmeceuticals and also can counsel the consumer regarding their use, interactions, side effects and toxicity. Pharmacists working in academia can improve theoretical knowledge of pharmacy students regarding both these supplements. Similar findings were reported in a study conducted in USA that highlighted the different roles a pharmacist can play to promote safe and effective use of dietary supplements including counseling to the consumer, quality assurance and ensuring safety while manufacturing, strict implementation of regulations, researches and education and training of students pharmacist regarding dietary supplements [21].

There are a lot of barriers faced by pharmacists while promoting safe and efficacious use of nutraceuticals and cosmeceuticals. The results of the study revealed that the majority of the respondents were of the view that one of the biggest and foremost issues is pharmacist knowledge and training. Some of the regulators mentioned that another important barrier is limited consumer knowledge. Some regulators believed that one of the challenges in promoting safe use of cosmeceuticals is lack of polices for manufacturing of cosmeceuticals. Few regulators were of the view that complete implementation of manufacturing standards is also a challenge in promoting safe and efficacious use of nutraceuticals. Lack of evidence-based data and literature regarding nutraceuticals and cosmeceuticals is also an important issue that needs to be addressed. Similar findings were reported in a study conducted in Australia that identified that the barriers involved in promoting safe and efficacious use of complementary medicines included lack of knowledge, lack of evidence based data and safety, lack of research skills, consumer's attitude and miscommunication with doctors [22]. Multiple strategies were recommended by regulators to overcome the challenges and barriers faced to promote safe and efficacious use of nutraceuticals and cosmeceuticals. Most of the respondents were of the view that involvement of manufacturers in development and implementation of policies should be increased. As manufacturers are the key stake holders, they can actively play their roles in the implementation of policies in a better way. Most of the regulators suggested that there is a need to train and educate our pharmacists at community and hospital level as only they are the ones who have close interaction with consumers, and they can counsel end users in a better way. Almost all the regulators highlighted that

policies regarding manufacturing and sales of nutraceuticals must be implemented in a strict way, as only then we can ensure safe and efficacious use of nutraceuticals. Many regulators recommended that pharmacists must play their active role in counseling of general public through any platform in order to promote safe use of nutraceuticals. Similar findings were observed in a study conducted in Australia which suggested collaborative efforts should be carried by stakeholders to overcome challenges and barriers [22].

Limitations of Study

This major limitation of the study was the use of small groups of stakeholders. Even though saturation was achieved, the limited number of interview participants precludes extrapolation of the results. Moreover, the present study was conducted in twin cities of Pakistan and results may not be generalized to the rest of the country.

Conclusion

The results of the present study concluded that nutraceuticals and cosmeceuticals are of great focus and concern for all the regulatory stakeholders. Majority of the respondents agreed that this is the era of nutraceuticals and cosmeceuticals but unfortunately these are most neglected topic in terms of research and knowledge. Multiple factors are responsible for affecting the safe and quality use of nutraceuticals and cosmeceuticals in Pakistan including lack of regulations for cosmeceuticals, lack of proper implementation of good manufacturing practices, lack of availability of evidence-based information, lack of knowledge among health care professionals, lack of defined role of pharmacist and lack of provision of evidence-based information regarding safety and efficacy of the product by manufacturer. Despite of the challenges and barriers faced by regulators related to safe and efficacious use of nutraceuticals and cosmeceuticals, they had constructive and practical ideas about how to embrace the current nutraceutical and cosmeceutical landscape and use the opportunity to develop professional roles that facilitates the appropriate and safe use of nutraceuticals and cosmeceuticals in Pakistan.

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