Review article

Practical Model for Expanding Quality & Efficacy Check of Pharmaceutical Products

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Overview about pharmaceuticals market in Sudan:

National Medicines and Poisons Board in Sudan is the responsible body for granting market authorization of pharmaceuticals as a requirement for all medicines distributed in public and private sector in Sudan. Based on recent statistics, end of 2010, there are about 3709 registered products in term of trade names that has been authorized [of which 11% were locally produces]. Based on the regulations, the registration renewal is required for the registered medicines every 5 years (1). The table below indicates the major indicators of pharmaceutical market in Sudan at the macro level (2).

Table 1: The major market indicators

Indicator	2007	2006	2005
	All values are in millions US$		
Total Sudan market value (all sectors)	285	234	222
Total market growth	21%	5%	7%
Total medicines supply value (paid)	213	164	152
Public sector medicines supply value	49	39	41
Private sector medicines supply value	164	153	111
Local production share in paid market	24.9%	23.8%	NA
CMS share in paid market	22.6%	19.3%	17.6%

The growth rate of the market in Sudan, especially after pace agreement, was very clear and many of pharmaceuticals companies expanded (or plan to expand) its establishment into the market not only in pharmaceuticals but also in other medical products.

The market in Sudan is favorable environment for generic pharmaceutical companies that based mainly in low income countries (especially: India, China, Egypt, Jordan, Syria) that represents significant figures in the market; see table below (2).

Table 1: Major countries contributing to Sudan market

Country	Share %	Region
Egypt	7.8	Arab
India	6.1	Asia
United Kingdom	5.0	Europe
Switzerland	3.2	Europe
Jordan	3.0	Arab
Germany	2.8	Europe
China	2.0	Asia

Importers (agents) and local producers are the major players in private sector in Sudan in addition to the direct (special) importation which represents only small part of the market in this sector. The total importation in 2007 was about 104 million US$ (no noticeable growth from 2005) by 77 agencies from 200 different companies and manufacturers. Sudan pharmaceuticals market could be described generally as generic market, in which the generic trades represents about 90-95% of the market in terms of items. More than 70% of the total export value is from Arab and Asian countries and accordingly the total value of the market is consider not large compare to the volume in term of quantities. As mentioned before the local products represent about 11% of the total registered items (3). When we consider all of this it will become clearly obvious that most of the products available in the market were imported from developing countries or countries with economies in transition. It will be very important to the "NMPB" to increase its capacity to detect and depict the existence of substandard medicines at different levels in the supply chain especially before it reach the end users (patients) to ensure safe and effective use of these medicines (4).

Statistics showed that among the top 15 medicines, that entered the market in Sudan 2007, all items were in the national essential list of medicines in terms of generic names. But at the same time and among the top 50 medicines 20% (10 items) were not essential medicines and their major source in general is CMS. About 21% of the medicines supplied through the public sector are locally produced compared to 8% only the year before (5).

Table 2: Top 15 medicines in the market 2006

Medicines			% of Share/Source		
Generic Name	**Strength**	**Dosage Form**	**Agents**	**CMS**	**Local**
1. Paracetamol	500 mg	Tablet	7	4	89
2. Metronidazole	250 MG	Tablet	2	10	88
3. Acetylsalicylic Acid	300 mg	Tablet	1	27	72
4. Amoxicillin	250 MG	Capsule	9	57	34
5. Diclofenac Sodium	25 mg	Tablet	15	14	71
6. Ampicillin + Cloxacillin	500 MG	Capsule	11	25	64
7. Chlorphenarmine Maleate	4 MG	Tablet	4	15	81
8. Chloroquine	200 mg	Tablet	0	0	100
9. Multivitamins & Minerals	-	Capsule	100	0	0
10. Folic Acid	5 MG	Tablet	86	0	14
11. Amoxicillin	500 mg	Capsule	15	20	65
12. Glibenclamide	5MG	Tablet	48	4	48
13. Mebendazole	100 mg	Tablet	4	4	92
14. Water for Injection	-	Injection	0	100	0
15. Ferrus salt	60-70mg	Tablet	0	100	0

Medicines registration outcomes in Sudan:

NMPB is the responsible body for issuing MA of different pharmaceutical products (beside poisons) and it is supported by standing committee that delegated from to approve the registration of human medicines (there is another committee for veterinary medicines). This committee consists of many experts in different sectors in health and pharmacy that approve or reject the submission request to register the pharmaceutical products. This is based adopted and published requirements and measures which were available in the department offices and on the federal pharmacy directorate web site. Up to this report there are about 3709 registered medicines in term of trade names (register by trade name using INN system). The following table summarized the registered items disaggregated by therapeutic groups versus the dosage forms:

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	212	21	38	18	8	3	300	08.1
Cardiovascular system	360	14	0	9	0	0	383	10.3
Respiratory system	33	3	34	5	20	0	95	02.6
Central nervous system	347	42	47	11	3	0	450	12.1
Infections	518	236	225	46	92	0	1117	30.1
Endocrine system	154	36	10	5	14	0	219	5.9
Obstetrics, gynecology, & urinary-tract disorders	25	14	1	4	4	3	51	01.4
Nutrition and blood	135	50	37	85	0	0	307	08.3
Musculoskeletal and joint diseases	199	28	19	18	32	0	296	08.0
Skin	7	3	6	25	119	0	160	04.3
Other	67	98	40	97	28	1	331	08.9
Total	2057	545	457	323	320	7	**3709**	
%	55.5	14.7	12.3	08.7	08.6	00.2		

Table 19: Summery table of registered products in Sudan

Current system of Post-marketing surveillance "PMS" in Sudan:

The PMS system in Sudan is generally similar to many other systems in developing countries. Its main component, and may be the only one, is the routine sampling and testing of the authorized products distributed at different components of the supply chain. The following described briefly the outlines of the system.

Selection of medicines:

Medicines selected for analysis and testing under the current system usually determined based on the following process:

1. Every month one pharmacological/therapeutic group normally targeted for testing based on the classification of BNF;
2. 40% of registered products within each group were randomly selected to be the major target for sample collection and the analysis. This usually represents 90% up to 95% of monthly analysis plan of PMS;
3. The remaining share of the products subjected to testing usually represents the items reported in the routine complaints receiving system. Normally assigned committee is responsible for the determination of products to be tested under this scheme out of all complaints received.

Complaint system:

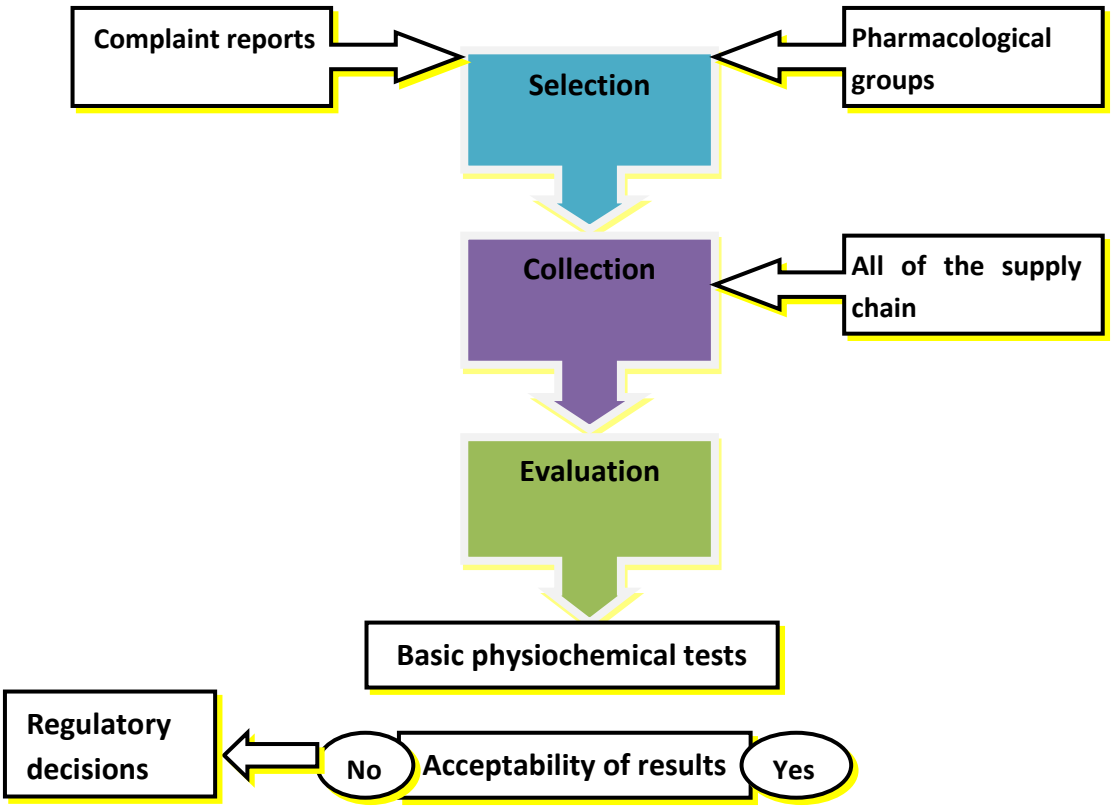
This system was established during 2006 and it used different communication tools including a hotline phone number (free of charge) in addition to direct acceptance of reports. These reports could arrive from different categories of the community including health professionals and the public as well. Certain forms used to describe details about the product and reported problem(s).

Quality evaluation:

The National Quality Control Laboratory "NQCL" is the responsible body for quality evaluation under this system. Certain communication plan usually applied between the PMS unit and the laboratory for follow-up and coordination. Quality evaluation checks under this system are basic physiochemical tests to evaluate the products under testing. The chemical analysis represents the main source of information to build the regulatory decisions (whether to recall, to revoke or any other decision). Studies indicated the weakness in NQCL mainly related to the capacity of the laboratory in different terms including human resources and the technical capacity (6). The capacity of the national laboratory to test medicines was a major component of plans during the last few years. In 2009 the total number of pharmaceutical products that have been tested (most of it were cosmetic products) was 2884 samples out of 2928 samples collected. According to results obtained 296 of items tested doesn't pass the quality specifications tests.

Looking at this system we can realize its passive nature, i.e. it depends basically on passive approach in selecting medicines/products for testing. There are no active measures in its components that adopt dynamic information to feedback the selection process of medicines and/or the regulatory decisions.

Figure 1: conceptual model of current PMS in Sudan



Detection rate & outcomes of the system:

On average, through the last 5 years, 9% of the tested items under this system were found not complying with reference specifications and this was varies from one year to another. The non-compliance problems vary in its nature ranging from small physical problems up to critical chemical contents problems.

The following table summarizes the details of medicines ***recalled*** from the markets during the last three years (3):

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	3	0	1	0	0	0	4	09.8
Cardiovascular system:	4	2	0	0	0	0	6	14.6
Respiratory system	0	0	2	0	0	0	2	04.9
Central nervous system	0	1	0	0	0	0	1	02.4
Infections	6	1	3	5	0	0	15	36.6
Endocrine system	4	0	0	0	0	0	4	09.8
Obstetrics, gynaecology, & urinary-tract disorders	0	0	0	0	0	0	0	00.00
Nutrition and blood	2	0	0	0	0	0	2	04.9
Musculoskeletal and joint diseases	3	1	1	0	0	2	7	17.1
Skin	0	0	0	0	0	0	0	00.00
Other	0	0	0	0	0	0	0	00.00
Total	22	5	7	5	0	2	**41**	
%	53.7	12.2	17.1	12.2	00.00	04.9		

Table 20: Summery table of recently recalled products

The following table summarizes the details of medicines ***revoked*** from the markets during the last three years (3):

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	7	0	0	0	0	0	7	11.7
Cardiovascular system	7	0	0	0	0	0	7	11.7
Respiratory system	3	0	0	0	0	0	3	05.00
Central nervous system	1	0	0	0	0	0	1	01.7
Infections	10	1	0	2	0	0	13	21.7
Endocrine system	12	0	0	0	0	0	12	20.00
Obstetrics, gynaecology, & urinary-tract disorders	1	0	0	0	0	0	1	01.7
Nutrition and blood	0	0	0	0	0	0	0	0.00
Musculoskeletal and joint diseases	5	0	0	0	1	0	6	10.00
Skin	0	1	0	0	3	0	4	06.7
Other	4	0	0	0	0	2	6	10.00
Total	50	2	0	2	4	2	**60**	
%	83.3	03.3	0.00	03.3	06.7	03.3		

Table 21: Summery table of recently revoked products

Note: the products in table 20 & 21 were not necessarily similar to each other.

Awareness about the system:

Getting back to the results obtained from health professionals' survey we found that only 42% of the pharmacists aware about this system. This relatively equal among different geographical areas surveyed, but it falls up to 14% in the peripheral areas in the city. Considering the experience of pharmacists responded, those with experience more than 5 years have more knowledge about the system better than other groups (especially those with 3-5 years of experience).

Category	Yes	No
All pharmacists (collective) n=82	42.8	57.0
1 year – 2 years (n=26)	44.0	56.0
3 years – 5 years (n=25)	33.3	62.5
More than 5 years (n=31)	64.7	53.3

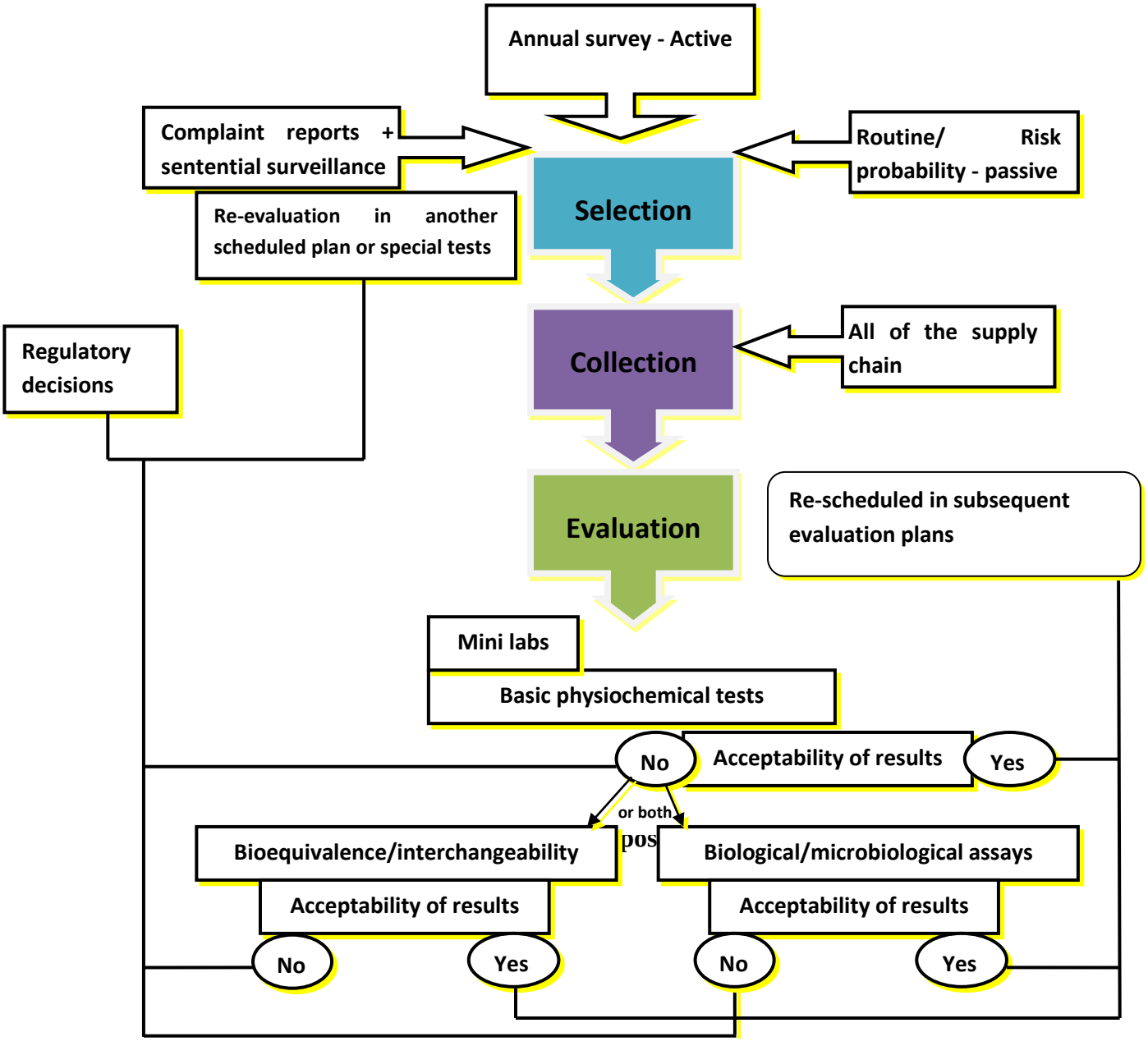
Among all of these pharmacists 38% have reservations about this system and its outcomes in detecting the low quality medicines and how it responds to the challenges in the field.

Expansion of the PMS system

Considering many facts that affect the value of current PMS system (such as the broad area in Sudan, capacity of NQCL and the limited financial resources) it become obvious that the current system need to be improved in an innovative way. The following graphical model indicates the suggested improvements of the system (compared to figure 17 of current model) by introducing more methods and approaches to get better outcomes.

According to the results obtained from previous study that investigated intensely the main causes of substandard medicines problem, the results pointed out different forms of problems with possibly different causes behind the detected cases. This started at the raw materials selection, through the manufacturing process, distribution and up to the storage (7). Accordingly, the way in which PMS system is designed should aim to reduce the manufacturing and trading of substandard. This form of such kind of vigilance should consider the process that checks the drug's identity, chemical integrity, physical stability, and biological activity, and exclude the possible damaging effects of inappropriate handling, packaging, and storage (8). On the other hand the combined interpretation of quality control

results with the clinical data or therapeutic outcomes of any product under this proposed scheme will support the regulatory decisions taken. This is particularly important in order to take overview picture for causes and effects of any problem and to include or exclude any potential factors that contribute to observed incident of substandard product.



Any strong PMS system should rely and based on strong drug monitoring information systems (9). This information system should be able to track the problems up to patients' level including the feedback from healthcare providers at different levels. For example, the system should consider and monitor regularly the information about the shifting practices of treatments. This indicates important information about the efficacy part of any product under observation. With regard to the generics that usually included in the process of shifting are generally similar to those tested under this research which indicates the importance and significance of this source of information. The proposed survey should also be able to bring such kind of information. In other aspect, the information system should differentiate between the complaints regarding the therapeutic process, that related to adverse reactions/events and that related to use of generics or any other sort of problems. By applying different reporting mechanisms the authorities will develop strong accumulated knowledge about the products, its manufactures and its distributors; what we can call "Product Profile". This should become a routine part of quality management system of pharmaceuticals products. Beside all of these, there are other potential sources of information need to be collected and considered in taking the regularity decisions (not only the results of PMS). This includes the following:

1. Pre-marketing surveillance test results;
2. Acceptability of the remaining shelf-life at time of receipt;
3. The history of the drug and its agent at NQCL before distribution;
4. The quality status at time of collection in accordance to Pharmacopeia;
5. The quality at the end of the shelf-life;
6. Drugs most frequently failed the tests;
7. The lost of potency among the time;

In this system the authorities should emphasize more on building the relations with health professionals form different categories. The results shows that only 15% and 10% of pharmacists and doctors respectively have ever notified the authorities by any information related to medicines they deal with. Even those who ever notified the authorities, most of them never received a feedback on their reports or notice any kind of action done as response to their reports (at least up to their knowledge). The role of pharmacy or health regularity bodies is very important and vital in the linkage between the professional practitioners and the products they use during their work. The feedback of the practitioners about the products

efficacy, safety and quality should be communicated effectively between the two sides. Conducting the proposed survey "described in the above model" under the umbrella of the "NMPB" (and the dissemination of annual reports based on this survey) should help in building the trust of professional practitioners towards the authorities and it will encourage them to report more frequently. This will have direct impact on improving the detection rate of low quality products circulated in the market. The system in this part should specify clearly the decision making mechanism related to the reported cases. This should help the reporters to know exactly how their reports will be treated and they will acknowledge the process the authorities take under this reporting mechanism.

Considering the critical importance of anti-infectives to public health in Sudan (10), it is now become very essential to investigate the problem around this therapeutic group as special part of the PMS system "specialized surveillance". All of the indicators from this research pointed out the volume of problems around products under this group. It is not only the resistance problems part but also its equivalence and other aspects. This proposed system appreciates the importance of establishing a monitoring system of "antimicrobials use" in the country including data about resistance (11). This system should ensure the development of strong mechanism that aim to monitor regularly the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors.

The reasons behind the recommendation to introduce the mini-labs strategy in this system was principally due to the fact that it could provide an inexpensive, low technology, non-laboratory-based testing option. It helps to assess product identity, disintegration, and drug content, which is of value in resource-limited settings like Sudan. When it is used by skilled persons, it provides an opportunity to identify substandard drugs in relatively inexpensive and quick process which is combined with other methods (12).

The approach by which this system designed and proposed is strong because it responds to problems that have been identified in most of PMS systems. In this regard the system will help the authorities because it is characterized by the following:

1. It is an effective quality monitoring system that use effectively the available resources;

2. It helps to increase the detection rate of substandard medicines;

3. It was based on improving the availability/sharing of information about the substandard medicines, the detected cases and the explanations behind that;
4. It provide advance and in-depth analysis of the detected cases;
5. It applies continuous improvement process (through research and development).

It is important to notice that handling of medicines quality judgments need to be combined with clinical outcomes analysis and ADRs surveillance and reporting. This should be a significant measure in order to avoid any subjectivity in the reported cases which need to be based on highly supported professionalism (13).

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