BERITA UBAT-UBATAN

NEWSLETTER OF THE DRUG CONTROL AUTHORITY, MALAYSIA

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Achievements of Drug Control Authority (DCA)

The National Pharmaceutical Control Bureau (NPCB) plays an important role as Secretariat to Drug Control Authority (DCA) and is responsible for ensuring therapeutic products that are approved in the market are of quality, efficacious and safe along with ensuring traditional and cosmetic products that are approved in the market are of quality and safe for consumers.The introduction of the online system for product registration and licensing by the National Pharmaceutical Control Bureau (NPCB) marks a new chapter in the history of pharmaceutical regulatory development in Malaysia. Malaysia was among the first regulatory agencies in the world to implement the online system for the application of product registration in 2002, starting with cosmetic products and later extended in stages to include the registration of products containing scheduled poisons (controlled items) and non-poison products (over-the-counter products) in July 2003 followed by traditional medicines in January 2004 and veterinary medicine products in August 2007.

Via the web-based system, known as QUEST, an acronym for Quality, Efficacy and Safety, companies are able to submit their applications for registration from any part of the world, any time of the day, and 365 days a year. The use of QUEST has proven to be beneficial to NPCB as well as to the local industry as it has streamlined the registration process and reduced bureaucracy. To further improve the services rendered by NPCB, the upgrading works of QUEST2 to QUEST3 is currently in progress.

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DRUG REGISTRATION

Since drug registration started in 1985, a total of 233,758 applications for product registration have been received. A total of 226,758 product status were recorded until December 2008 due to backlog cases and from there, a total of 207,911 (91.3%) products were registered and 18,847 (8.7%) applications were rejected by the Drug Control Authority (DCA) for various reasons (Please refer to Figure 1).

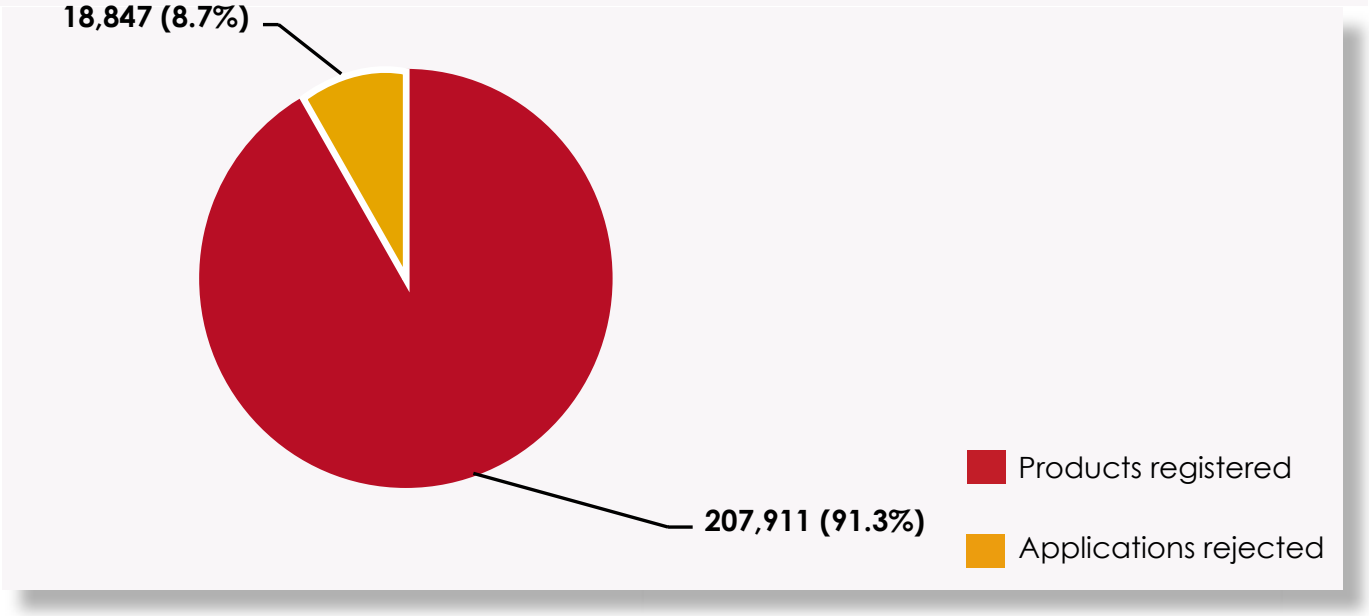


Figure 1: Statistics on Product Registration (1985-2008)

A total of 33,444 applications for product registration were tabled to the DCA in the year 2008. After a thorough review of each submission, 32,165 products were registered by December 2008. Of these, the number of prescription drugs, non-prescription drugs, traditional products and cosmetics registered by the DCA were 409 (1.2%), 272 (0.8%), 953 (3.0%) and 30,531 (95.0%) respectively (Please refer to Figure 2).

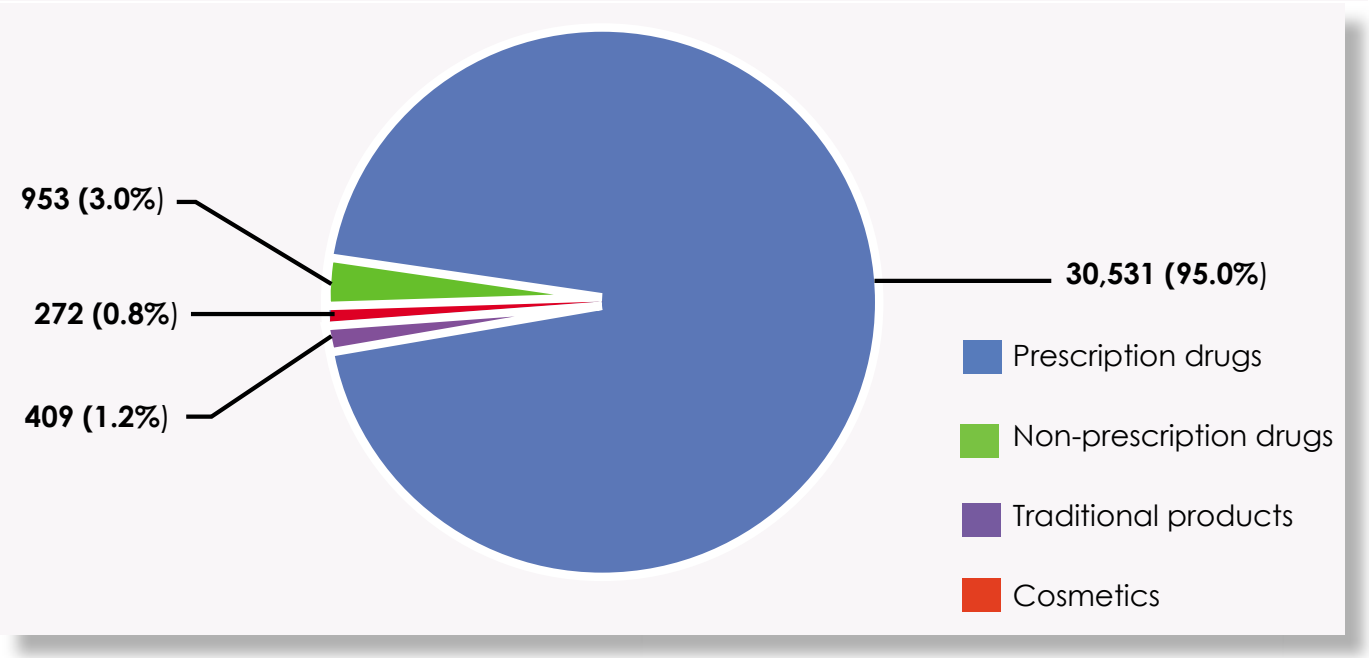


Figure 2: Products Registered by the DCA (2008)

Of the total cumulative number of products registered by the DCA, 56,841 are locally manufactured while 151,060 are imported (Please refer to Figure 3).

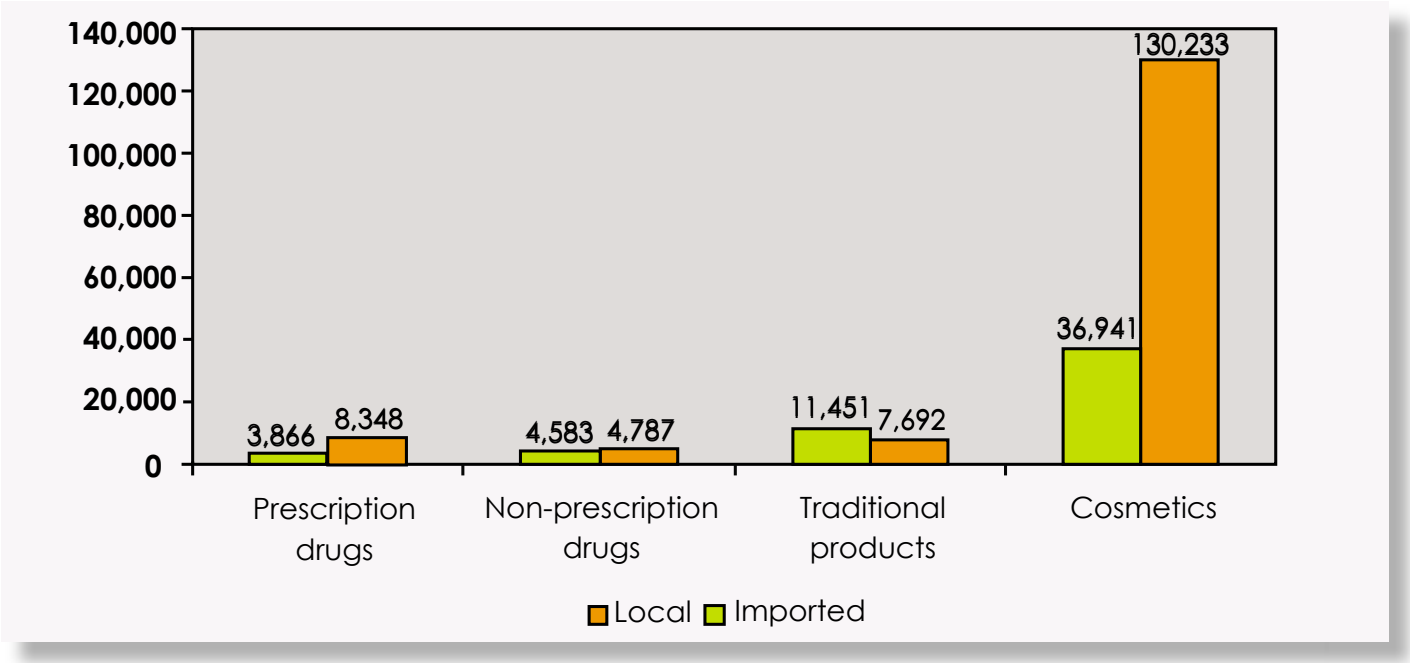


Figure 3: Cumulative Number of Products Registered (1985-2008)

POST-MARKET SURVEILLANCE

As part of the regulatory process, in order to ensure continued compliance to safety, efficacy and quality, registered products are subjected to testing under the post market surveillance programme. For this purpose, a total of 2,272 registered products were sampled in the year 2008. Based on the outcome of the laboratory testing, 112 product batches were subjected to Degree III product recalls (i.e. within 30 days) due to quality defects. The recalls involved 10 (9.0%) prescription drugs, 7 (6.3%) non-prescription drugs, 92 (82.1%) traditional products and 3 (2.6%) cosmetics (Please refer to Figure 4). The registrations of 22 products were cancelled as the samples tested were found to be adulterated with scheduled poisons.

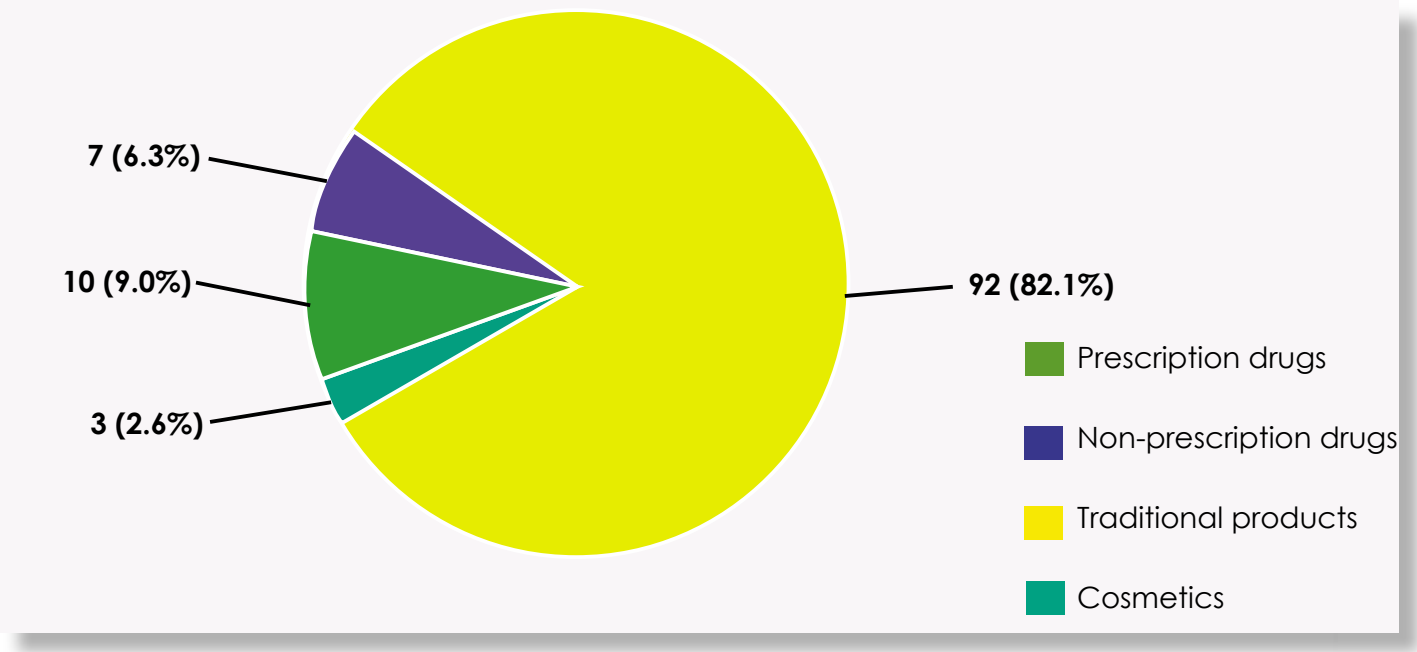
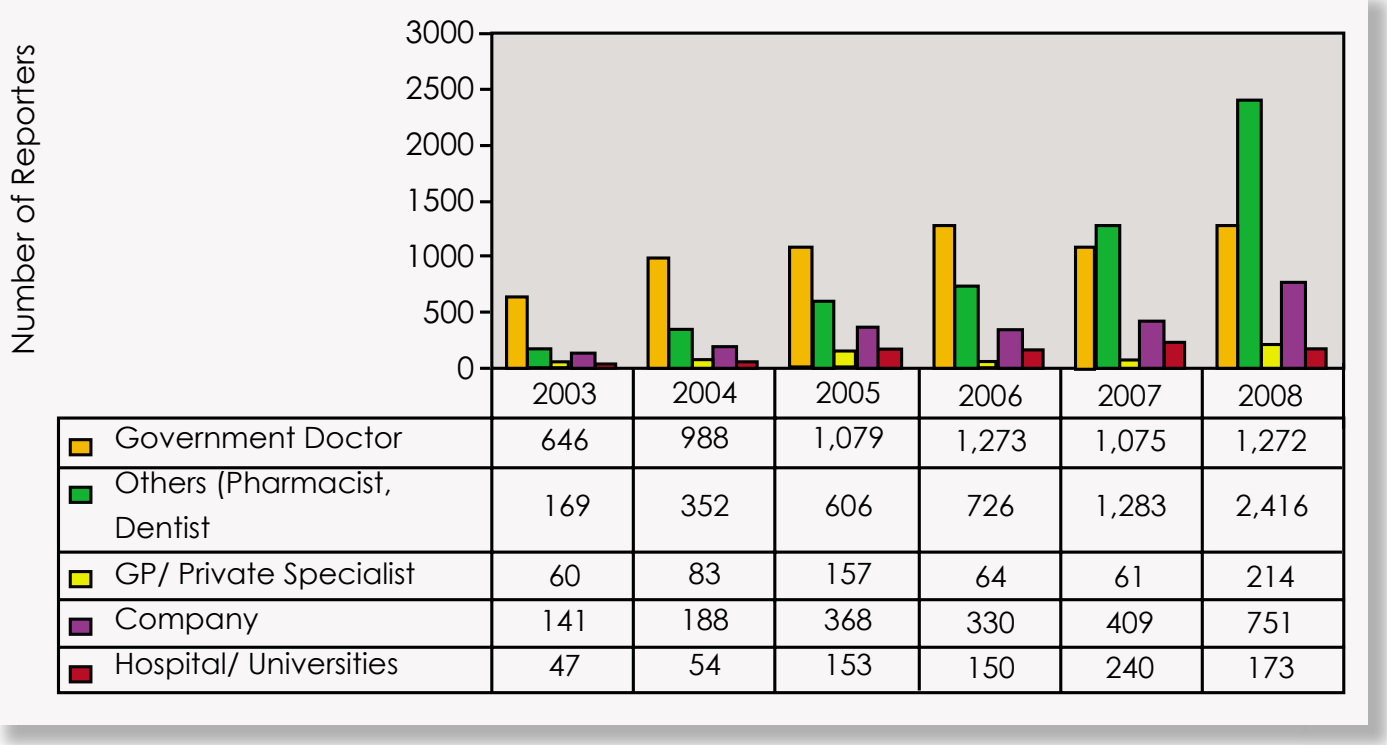


Figure 4: Product Batches Subjected to Degree III Product Recalls (2008)

2,375 labels and package inserts were also checked under the surveillance programme. Warning letters were issued for 293 products which were found to be non-compliant with the labeling requirements. The NPCB also investigated 468 product complaints submitted by health professionals and the general public which subsequently led to punitive actions taken such as recalls being conducted for some of these products from the market.

ADVERSE DRUG REACTION MONITORING

In 2008, a total of 4,826 adverse drug reaction (ADR) reports were received, a 58% increase as compared to the previous year. Of this, 4,487 reports were evaluated and subsequently 4,382 reports were submitted to the WHO ADR Monitoring Centre in Uppsala, Sweden. An analysis of the submitted ADR reports showed that slightly more than 50% and 26% were from pharmacists and doctors in the government sector respectively (Please refer to Figure 5).



	2003	2004	2005	2006	2007	2008
Government Doctor	646	988	1,079	1,273	1,075	1,272
Others (Pharmacist, Dentist	169	352	606	726	1,283	2,416
GP/ Private Specialist	60	83	157	64	61	214
Company	141	188	368	330	409	751
Hospital/ Universities	47	54	153	150	240	173

Figure 5: Analysis of Adverse Drug Reaction (ADR) reports based on category of reporters (2003-2008)

QUALITY CONTROL

On the aspect of quality control, a total of 55,479 tests were done on 4,376 samples, from which 1,487 (34.0%) samples were for applications for registration, 2,296 (52.5%) samples from surveillance activities, 132 (3.0%) samples arose from product complaints, 408 (9.3%) samples were result of enforcement activities and 53 (1.2%) samples were from other sources (Please refer to Figure 6).

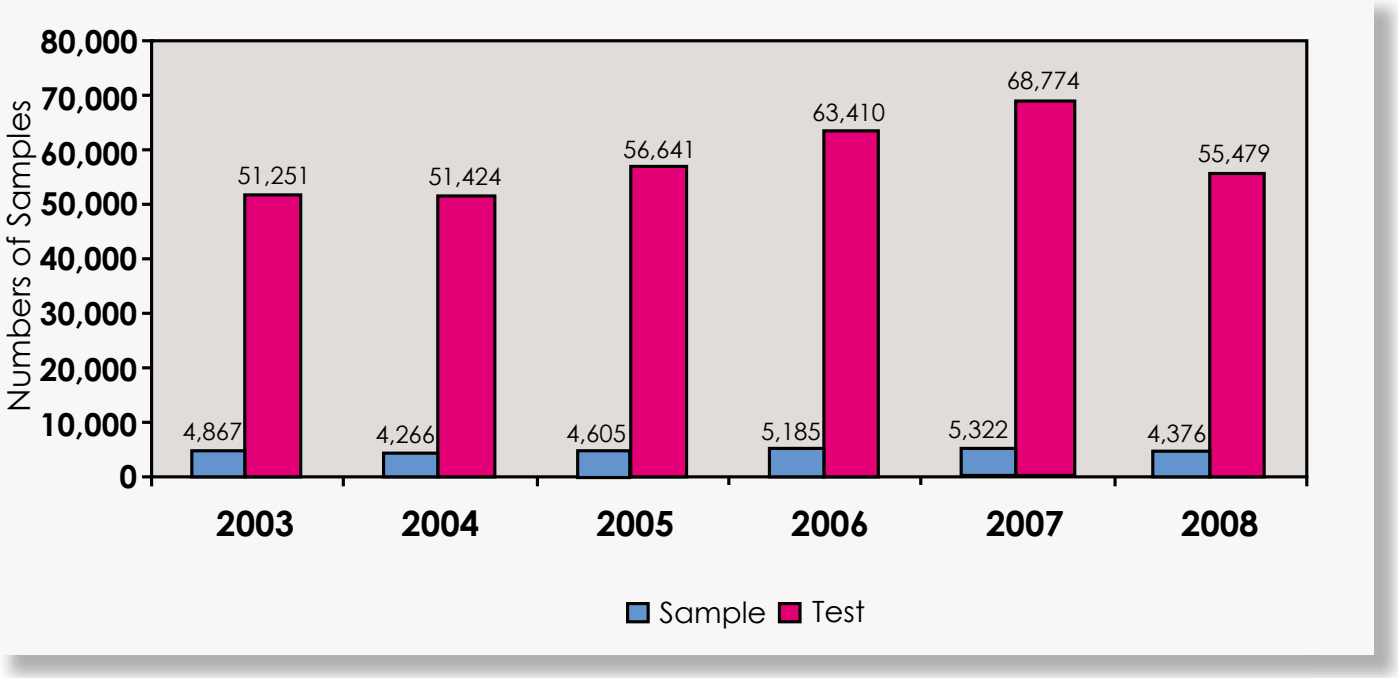


Figure 6: Statistics on Tests of Samples (2003-2008)

INSPECTION AND LICENSING

In the year 2008, 245 manufacturing premise licenses were issued of which 69 (28.2%) were for pharmaceutical products and 176 (71.8%) were for traditional medicines. 377 import licenses were issued, comprising of 223 (59.2%) pharmaceutical and 154 (40.8%) traditional licenses. As for wholesalers' licenses, 1,031 were issued of which 479 (46.5%) of these licenses were issued to wholesalers of products containing scheduled poison drugs and 552 (53.5%) licenses were issued to wholesalers dealing with non-poisons, traditional medicines and cosmetics (Please refer to Figure 7).

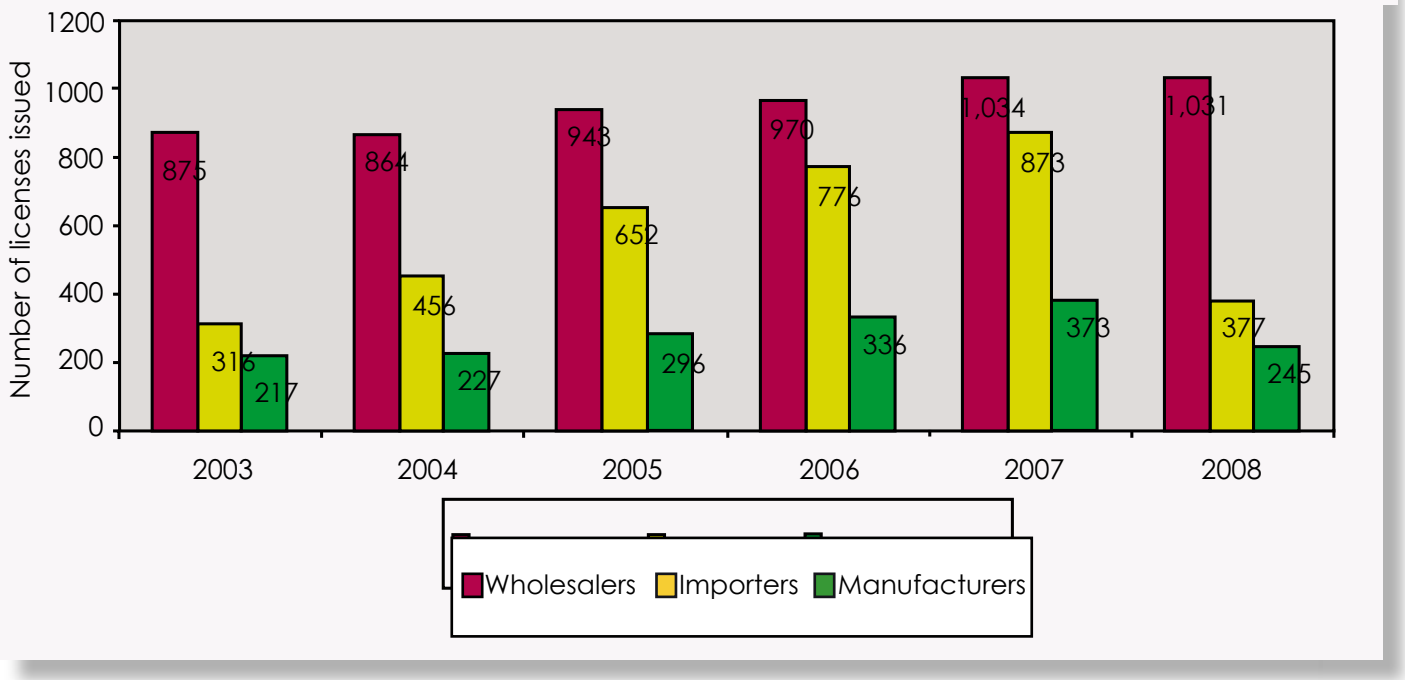


Figure 7: Statistics on Licenses Issued (2003-2008)

PUBLICATION

NPCB also publishes the Drug Control Authority 'Berita Ubat-Ubatan' to disseminate drug and regulatory information to health professionals and the industry. In 2008, the Centre for Organisational Development of NPCB received 2,322 enquiries through telephone, e-mail, facsimiles and letters from government agencies, companies and the general public.

INTERNATIONAL INVOLVEMENT

The NPCB continues to play an active role in the harmonization efforts through the ASEAN Consultative Committee for Standards and Quality (ACCSQ), Pharmaceutical Product Working Group (PPWG), Traditional Medicines and Health Supplements Product Working Group (TMHS PWG) and ASEAN Cosmetic Committee (ACC). Other international involvements include facilitating the fast-track ASEAN healthcare integration and EC-ASEAN Economic Cooperation on Quality, Standards and Conformity Assessments, as well as other PIC/s activities. The NPCB has also participated in other international consultations such as Technical Meetings and initiation of Bilateral Arrangements with ASEAN member countries as well as participation in the Malaysia-US Free Trade Agreement (MUSFTA) negotiations.

VISITS AND TRAINING OF VISITORS FROM OVERSEAS

Throughout the year 2008, the NPCB received a total of 24 international visitors from various countries such as Ethiopia, Indonesia, Myanmar, Nepal, Sudan and Uganda. Those who came on educational visits were given training according to their respective specific needs. Training given was in the aspect of quality control, product registration, good manufacturing practices and licensing or pharmacovigilance and surveillance.

FUTURE PLANS

i. Intensification of post-market surveillance
   - To intensify surveillance activities with the aim of combating problems associated with adulteration, counterfeits and product authentication as well as to promote public health protection through education and awareness.
   - To further enhance post-marketing surveillance and reduce emphasis on pre- market assessment especially for cosmetic products in Malaysia.

ii. Developing human resource and maintaining staff and expertise
   - To ensure staff acquires sufficient knowledge and become experts in their area of work.
   - To ensure the creation of sufficient senior/promotional posts so as to absorb those who are promoted, thereby providing some incentives for staff to stay in the NPCB.
   - To find ways to reduce attribution rate when compulsory service is over.

iii. Emphasizing Information and Communication Technology (ICT) culture within the organization
   - The NPCB continues to strive towards upgrading its ICT infrastructure. Under the 9th Malaysian Plan (2006-2010), the NPCB has been granted allocation that will be used for upgrading the present on-line system QUEST2 to QUEST3.
   - To increase exposure of staff to IT

iv. Additional emphasis on training programme
- There is additional emphasis on training programmes for staff to ensure their respective specific needs are met.
- Efforts will be undertaken to increase use of consultants for local training and increase overseas attachment for staff

v. Overall development plan for Quality Management System (QMS)
- In terms of quality control, the NPCB, which has been successful in attaining the MS ISO 9001:2000 certification, will continue its efforts towards obtaining ISO 17025 certification for the Centre for Quality Control.
- Efforts will be undertaken by the NPCB to become a member of Organisation for Economic Co-operation and Development (OECD)
- The NPCB also strives to enhance the Quality Management System (QMS) of the NPCB and to reinforce Pharmaceutical Inspection Cooperation Scheme (PIC/s).

vi. Reinforcing cooperation with other regulatory agencies
- In years ahead, the NPCB hopes to be strengthened through reinforcing cooperation with other regulatory agencies by sharing information on registration of New Chemical Entities and Biotechnology products especially in view of Data Exclusivity implementation, sharing of GMP reports so that it will reduce the cost of foreign inspections and sharing information on surveillance activities especially on imported products, thus reducing the cost of laboratory testing.

Involving Consumers in Medicines Surveillance - An updated report from Malaysia

The involvement of consumers in medicines surveillance can contribute towards the detection of :-
- Quality defects
- Ineffective products
- Adverse drug reactions
- Fraudulent or misleading claims
- Inappropriate product labeling
- Suspected counterfeit
- Unregistered products

Since the initiation of the pilot study in March 2007, up to this date, the National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia has received 53 reports from consumers. The reports that have been received so far cover the entire spectrum of the areas stated above.

Two (2) complaints on **quality defects** were received. For such complaints, where product samples can be obtained, laboratory tests would be conducted if warranted. The product registration holder would also be notified so that the company could do the necessary investigations. The complaints noted above were on generic products and testing confirmed that the products conformed to specifications.

There was **one (1)** report for **ineffective product**. The product was an anti cancer drug and the patient experienced a rapid progression of prostate cancer. The product registration holder was asked to investigate. According to data that had been provided to NPCB, the active ingredient level was tested and found to comply with specifications. No further action was taken since NPCB does not have the facilities to run tests on cytotoxic drugs.

Nineteen (19) reports came from consumers who had experienced **adverse drug reactions**. Most of the adverse drug reactions reported were associated with the use of traditional medicines, health supplement and cosmetics, i.e. products bought over the counter by consumers. Samples of products suspected could have been adulterated with chemical therapeutic ingredients were screened for their presence based on product use and claims. Appropriate regulatory action would be taken if confirmed positive. **One such complaint resulted in the deregistration of a traditional product that had been adulterated with Fluoxetine**.

There were also unregistered products which had been reported to have caused ADRs and such products if identified would be referred to the Pharmaceutical Enforcement Division for further action.

Consumers had also submitted complaints for **fraudulent or misleading claims**. These reports included complaints of cosmetic products which carried medical claims. In such instances, warnings were issued to the companies responsible for placing the cosmetics on the market to change their labels to comply with the cosmetic guidelines for labeling. If there were unregistered products, the information would be forwarded to the Pharmaceutical Enforcement Division for further action.

Besides fraudulent or misleading claims, there were also complaints made for **inappropriate product labeling. Four (4)** such reports were received where consumers reported on

- labels of products without registration number stated,
- label used was different from the registered label,
- fake registration numbers (MAL No).

Checks were conducted on all such complaints and information forwarded to the Pharmaceutical Enforcement Division of all products identified as unregistered. Warnings have been issued to product registration holders who have been non compliant to labeling requirements.

There was **one (1)** report on **suspected adulteration** in which a patient experienced muscle ache. Previously the patient was on Lovastatin and had experienced the same effect. After taking a Red Yeast Rice product, he again experienced the muscle ache and therefore suspected that the product could be adulterated with Lovastatin. The sample given was tested and confirmed to contain a trace of Lovastatin. However the amount of Lovastatin was so low, it was concluded that it was naturally present in the Red Yeast Rice and not an added ingredient. In this instance no further action was taken

All in all, a total of **sixteen (16)** reports on **unregistered products** were submitted by consumers. All of these reports were forwarded to the Pharmaceutical Enforcement Division for further action

Most of the reports received were valid with good documentation by the consumers. But still, there were reports which could not be assessed because the complainant was unable to furnish the necessary information needed. Most of the consumers who had reported to the NPCB supplied contact numbers and were willing to furnish further information if required.

From the summary given above, consumers do have a role in surveillance and can help in ensuring that products in the market are safe and of quality. Increased consumer awareness and vigilance in the monitoring of medicinal and cosmetic products that they use is a natural extension of their involvement in personal health management and care. Hence, can be a vital tool in targeted surveillance of "problem" products.

REPORTS REGARDING LOCAL HEPARIN PRODUCTS DETECTED WITH CONTAMINATED OVER-SULPHATED CHONDROITIN SULPHATE

The DCA at its 209th meeting on the 25th September 2008 has decided to forbid the sale of Unihepa products until the required tests prove that their products are not contaminated.

The registration of the following Duopharma (M) Sdn. Bhd. products have been suspended and stocks available in the market are to be recalled back:
UNIHEPA 5000 IU/ML INJECTION (MAL20051411A)
UNIHEPA 50 IU/5ML INJECTION (MAL20012728A)

ACTIONS TAKEN BY U.S. FOOD AND DRUG ADMINISTRATION (FDA) ON PRODUCTS MANUFACTURED BY RANBAXY LABORATORIES LIMITED, INDIA (FROM TWO MANUFACTURING SITES, DEWAS AND PAONTA SAHIB) DUE TO POOR COMPLIANCE TO GOOD MANUFACTURING PRACTICE (GMP)

On 16th September 2008, U.S. Food and Drug Administration (FDA) issued a warning letter to Ranbaxy Laboratories Ltd., India and also an import alert towards generic products manufactured by Ranbaxy Laboratories Ltd. Dewas, India and Ranbaxy Laboratories Ltd. Paonta Sahib, India.

The warning letter was issued on the basis of violations of U.S. current Good Manufacturing Practice (cGMP) requirement by manufacturing sites in Dewas and Paonta Sahib, India. Because of the extent and nature of the violations, the FDA also issued an import alert under which U.S. officials may detain at the U.S. border, any active pharmaceutical ingredients (API) as well as sterile and non-sterile finished drug products manufactured at these Ranbaxy facilities and offered for import into the United States.

These proactive measures are taken by the FDA in order to assure that all drugs that reach the American public are manufactured according to cGMP requirements. However, this action does not involve recalling the products from the market as the FDA has no evidence to date that Ranbaxy has shipped defective products.

The DCA has registered products manufactured by Ranbaxy Laboratories Ltd from both manufacturing sites. As such, the action recommended to be taken is to have:

- Continuous surveillance to ensure products brought in from India, particularly from the

manufacturing sites of Dewas and Paonta are of quality, efficacious and safe to use. The NPCB will also continue to communicate with agencies like the FDA and WHO to obtain updated reports and development regarding this issue as well as with the registration product holder, Ranbaxy (M) Sdn Bhd, regarding corrective actions taken to ensure the highest degree of compliance to Good Manufacturing Practice (GMP).

- No actions will be taken towards importation and usage of the registered products at the moment. Only surveillance will be done and discussions with other agencies regarding current actions taken as well as random sample taking will be done for products manufactured by Ranbaxy, India.

- For registration applications still in evaluation, the processing will be postponed until the feedback obtained shows that all corrective actions have been implemented by Ranbaxy Laboratories Ltd in those manufacturing sites.

REGISTERED PRODUCTS THAT HAVE PROBLEMS WITH BIOEQUIVALENCE (BE) STUDIES REPORT

The DCA at its 209th meeting on 25th September 2008 has agreed that:

- For registered products whereby it is confirmed that the company will not be doing Bioequivalence (BE) studies but has appealed for registration to be retained for purpose of 'For Export Only' will not be considered and registration of those products will be cancelled.

- For registered products in government tender list, whereby it is confirmed that the company concerned will not be doing BE studies, the registration of those products will be cancelled and the Pharmaceutical Services Division, Ministry of Health Malaysia will be informed the list of products that have BE studies report to replace the cancelled tender products.

- For registered products containing active ingredients listed in the BE requirement list but do not have BE studies report after the enforcement date (Local products: 31st December 2007; Imported products: 1st June 2007), the registration of those products will be suspended until satisfactory BE reports are submitted to the DCA.

ADVERSE EFFECTS RELATED TO TENDONITIS AND TENDON RUPTURE IN PACKAGE INSERTS OF ALL ANTIMICROBIAL SYSTEMIC FLUOROQUINOLONES GROUP PRODUCTS

The DCA at its 210th meeting on the 27th November 2008 has decided to further clarify on the available statement about adverse effects related to tendonitis and tendon rupture for all antimicrobial products from fluoroquinolones group for systemic usage only **(oral preparations and injection forms)**. The statement is as follows:

'Special warnings and precautions for use'

Musculo-skeletal system:

"The risk of developing fluoroquinolone-associated tendonitis and tendon rupture is further increased in people older that 60, in those taking corticosteroid drugs, and in kidney, heart, and lung transplant recipients. Patients experiencing pain, swelling, inflammation of a tendon or tendon rupture should be advised to stop taking their fluoroquinolone medication (to specify the active ingredient) and to contact their health care professional promptly about changing their antimicrobial therapy. Patients should also avoid exercise and using the affected area at the first sign of tendon pain, swelling, or inflammation".

Note: Tropical preparations like ophthalmic and otic preparations are exempted from this warning statement

CONTACT & MAP

ORGANISATION	TEL-EXT
National Pharmaceutical Control Bureau	+ 603 - 7883 5400
Centre for Product Registration	5487
Section 1 Generic Medicines Section	5490
Section 2 Complementary Medicine & Veterinary Section	5489
Section 3 New Drug Section	5522
Section 4 Biotechnology Section	5518
Section 5 Regulatory Coordination Section	5502
Section 6 Non-Prescription Medicines Section	5497
Centre for Post Registration	5538
Centre for Organisational Development	5553
Centre for Compliance and Licensing	5564
Centre for Quality Control	5429
(i) Reference Standard Unit	5468
(ii) Laboratory Services Unit	5477
(iii) Pharmaceutical Chemistry Testing Section	5450, 5456, 5462
(iv) Bio-Pharmaceutical Testing Section	5442, 5446
(v) Natural Product Testing Section	5471
Administrative Centre	5412

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