Adverse drug Reaction (ADR) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. If it is encountered, it should be reported for all products registered by the Drug Control Authority (DCA) i.e. pharmaceutical products as well as traditional medicines. Spontaneous reports of suspected adverse drug reactions received from healthcare professionals should be reported even if the product registration holder does not agree with the reporters' assessment of a possible causal association or if the reporter has not provided a causal assessment. All adverse reactions should be considered reportable according to the requirements outlined in these guidelines regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product.
Therefore, in order to produce a quality report, on May 2014, Drug Information Services, Pharmacy Department, Putrajaya Hospital had organized and ADR Workshop which was made compulsory for all Pharmacists of Putrajaya Hospital. It was conducted in four sessions, so as not to affect any of pharmacy services. The objectives of this workshop are; to enhance the quality of reporting ADR; to encourage pharmacists to report ADR by developing skill and confidence in the reporting process; and to increase awareness among pharmacists to report any adverse event.

The workshop was started with introduction to ADR, followed by reporting a quality report. As we all know, in order to report an ADR case, Report on Suspected ADR form or the blue form need to be filled, however in order to have a quality ADR report, Naranjo Algorithm Scale form, Clinical Manifestation of ADR form and Chronology of event must be attached together as supporting documents. Furthermore, the participants were also introduced to Hartwig’s Assessment, as a tool to categorize the severity of the ADR. Last but not least, there were hands on conducted on three real ADR cases that occurred in Putrajaya Hospital. Hopefully, with this workshop, all pharmacists would be able to produce a good quality report and promote ADR reporting among pharmacists.

References:
Antihistamine or \( H_1 \) antagonist plays a role in the management of various conditions. It has been used as a sedative, an anti-emetic, as well as in the treatment of allergic rhinitis, atopic dermatitis, urticaria, cough and cold, and the list goes on.\(^1,2\) Despite its widespread use, several adverse effects have been reported since its discovery. The reported adverse effects include central nervous system (CNS) related effects like drowsiness, fatigue, impaired concentration and memory which may result in detrimental effects on the learning in children, as well as impairment on the ability of adults to work, drive and operate machineries, anti-cholinergic effects such as dry mouth and constipation, and in more severe cases respiratory depression, coma or even death.\(^3,4\) As a result, most antihistamine products are not recommended for children aged 2 years and below.

It is said that the CNS-related adverse effects are more common with the older first-generation antihistamines due to their extensive penetration across the blood-brain barrier, thus giving rise to the name “sedating antihistamines”. Examples of sedating antihistamines include chlorpheniramine, diphenhydramine, promethazine and triprolidine.\(^1,3\) Meanwhile, the newer second-generation antihistamines have been known as “non-sedating antihistamines” as they are less likely or do not cross the blood-brain barrier, thus minimizing their effects on the CNS. Examples of non-sedating antihistamines include loratadine, cetirizine and fexofenadine.\(^1,3\)

As mentioned earlier, most antihistamine products are not recommended for children aged 2 years and below. Studies have also reported potentially detrimental effects with the use of antihistamines, particularly the first-generation antihistamines in young children. In this article, we will be discussing the safety of...
some of the antihistamines in children, particularly those which are also available as syrup formulation in Hospital Putrajaya.

**Promethazine**

Promethazine belongs to the group of phenothiazines. It is a long-acting antihistamine with mild anticholinergic effects and some antiserotonin effects. Promethazine has marked effect on the CNS, leading to its use as an antiemetic, hypnotic, tranquiliser, as well as a potentiator of anaesthetics, hypnotics, sedatives and analgesics. However, promethazine has a wide range of CNS-related adverse effects which may affect usual performance at work and daily activities. It is contraindicated in children aged 2 years and below.\(^4\,^5\,^6\)

Based a study conducted back in 1979, four infants who received promethazine were found to be victims of the sudden infant death syndrome (SIDS).\(^5\) Additional case reports were gradually added to the literature, further strengthening the relationship between phenothiazines and respiratory adverse effects in infants. Another study conducted in 1991 reported promethazine-induced apnoea in a 2-month-old girl.\(^5\) The suggested mechanisms for promethazine-induced apnoea include a direct central respiratory depressant effect, and antagonism of central dopaminergic receptors leading to raised levels of endogenous opioids which may cause respiratory depression. As promethazine undergoes extensive hepatic metabolism, particularly via CYP2D6 enzyme, the lack of CYP2D6 in infants could be the reason respiratory depression is more pronounced in infants, particularly premature neonates.\(^5\,^6\) Promethazine is available in HPJ as Promethazine HCl 5mg/5ml Syrup.

**Diphenhydramine**

Diphenhydramine is an antihistamine with anticholinergic and sedative properties. It is commonly given to children as a cough syrup and its sedative properties was thought to aid in sleeping.\(^7\,^8\) According to a study conducted by Paul et al., the two commonly prescribed cough medications including diphenhydramine did not show a superior benefit when compared with placebo for outcomes of the study such as improvement in nocturnal cough and sleep quality.\(^7\)
Some of the reported adverse effects of diphenhydramine include CNS-related effects such as sedation and disturbed coordination, as well as anticholinergic effects like thickening of bronchial secretions and constipation. Diphenhydramine is contraindicated in neonates and premature infants. Diphenhydramine is available in HPJ as Diphenhydramine HCl 14mg/5ml Elixir and Diphenhydramine HCl 7mg/5ml Elixir.

**Chlorpheniramine**

Chlorpheniramine is a potent antihistamine. Its pharmacological actions include inhibition of histamine on smooth muscle, capillary permeability and thus reduction of oedema in hypersensitivity reactions. Hence, it is commonly indicated for symptomatic control of all allergic conditions responsive to antihistamines, including hay fever, vasomotor rhinitis, urticaria, angioneurotic oedema, food allergy, and insect bites. Chlorpheniramine is also indicated for the symptomatic relief of itch. Some of the common adverse effects of chlorpheniramine are sedation, nausea and dry mouth. Chlorpheniramine is not recommended, but not contraindicated for children aged 1 year and below. Nonetheless, children are more susceptible to neurological anticholinergic effects and paradoxical excitation such as restlessness and nervousness.

A review of the adverse events associated with the use of antihistamine in children for cough and cold has shown reports of mortality associated with the use of antihistamines. Out of 69 fatal cases identified, 27 were associated with the use of chlorpheniramine, and majority of the cases occurred in children aged below 2 years. The reasons for the occurrence of overdose and drug toxicity include the use of multiple similar products, medication error such as wrong dose given, and accidental exposures. Chlorpheniramine is available in HPJ as Chlorpheniramine Maleate 2mg/5ml Syrup. Generally, it is recommended that clinicians take into account the necessity for use and balance the potential risks and benefits of antihistamine when prescribing any of the antihistamines to infants and young children. When dispensing any antihistamines to a patient’s parents, it is also important to emphasize on the age group for which the product is indicated for and the correct dose to be administered to prevent unintentional overdose.
References:

6. Promethazine Winthrop data sheet
8. MIMS Malaysia. Benadryl Full Prescribing Information.
TB is an important disease both globally and in Malaysia. In 2010, there were an estimated 8.8 million new cases of TB globally with 1.1 million deaths among HIV-negative cases of TB and an additional 0.35 million deaths among people who were HIV-positive. Locally, the incidence was 81.4 per 100,000 populations in year 2010. The number of new TB cases in the country increased from 15,000 in 2005 to 19,251 in 2011. While PTB was the commonest form of TB in Malaysia, extrapulmonary TB (EPTB) still posed a threat.

Based on the medical news, Health Minister Datuk Seri Dr S. Subramaniam said there are 10,007 tuberculosis (TB) cases were reported for the first five months this year 2014. Of this number, only 8,568 of Malaysians involved while the rest were foreigners. Besides, he said that there were many factors which caused the spread of TB, and the presence of foreigners in the country was one of the reasons.
High risk groups

a) Close TB contacts and nonhousehold contact
b) Immunocompromised patients
   - Diabetes Mellitus
   - Human Immunodeficiency Virus Infection
   - Chronic obstructive pulmonary disease
   - End stage renal disease
   - Malnutrition
   - Use of immunosuppressant in rheumatoid arthritis
c) Substance abusers and cigarette smokers
   - drug users (eg: illicit, intravenous and hard drugs)
   - intravenous drug users
   - excessive alcohol consumption
   - current smoker
d) people living in crowded situation
   - homelessness
   - history of incarceration
   - institutionalization
     (eg: homes for the elderly and shelters)
   - prison

Clinical features

a) Pulmonary TB
   - Persistent cough lasting for 3 weeks or more with no other explanation
   - Weight loss/anorexia
   - Fever
   - Night sweats
   - Hemoptysis
   - Chest pain
   - Fatigue
b) Extra-pulmonary TB
   - based on the organs involved and may be nonspecific
   - leukocytosis
   - anemia
   - hyponatremia
Investigations

- Mantoux Tuberculin Skin Testing
- Acid-fast bacilli (AFB) smear and culture by using patient’s sputum
- HIV serology in all patients with TB and unknown HIV status
- Chest radiograph
- Computed tomography (CT) scan

Treatment

Six-month regimen consisting of two months of daily isoniazid, rifampicin, pyrazinamide and ethambutol followed by four months of daily isoniazid and rifampicin is recommended as standard treatment for pulmonary TB. All the doses of TB drugs are based on patient body weight. Rifampicin should be rounded to higher recommended dose if tolerated. Besides, if ethambutol is contraindicated, streptomycin can be substituted. Studies show that over 90% of new cases of TB are drug sensitive and can be cured with standard therapy. The initial phase of treatment should be continued until full susceptibility is confirmed, even if this is beyond two months if the sputum culture confirms *M. tuberculosis* but drug sensitivity results are still awaited.

As for extra-pulmonary TB, all extrapulmonary tuberculosis should be treated with antituberculosis treatment for a minimum of six months except for bone (including spine) and joint tuberculosis for 6 – 9 months and tuberculous meningitis for 9 - 12 months based on Clinical Practice Guideline Malaysia.
Directly observed therapy (DOTS), Short Course

Patient adherence to appropriate drug treatment is a major determinant of treatment success. If there has been good adherence with the appropriate drug regimen, relapse is uncommon in those with fully drug-sensitive TB (0–3%). Rifampicin preparations impart an orange-red colour to bodily secretions and fluid, including urine, and this can serve as an indication whether patients are taking their medication.4

Based on CPG tuberculosis, DOT should be patient-centered, incorporating negotiations, and patient’s characteristics and preferences. Prompt reminders should be sent to TB patients if they are not compliant to treatment. Home visit by healthcare workers should be carried out if patient fail to follow the regimen. Besides, trained non-governmental organisation staff, community members and peers should be used to reinforce compliance to treatment and provide support to patient suffering from tuberculosis.

References:

1) Management of tuberculosis (CPG Malaysia)
2) Malaysian Medical News: 10,000 TB cases reported as of May. Online. http://malaysianmedicine.blogspot.com/2014/06/10000-tb-cases-reported-as-of-may.html
Medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the healthcare professional, patient or consumer. It may be related to professional practice, healthcare products, procedures and systems including; prescribing, order communication, product labeling, packaging, compounding, dispensing, distribution, administration, monitoring and use. Medication errors can be committed (or contributed to) by anyone who handles medicine which are physicians/doctors, dentists, pharmacists, other healthcare providers, patients, caregivers, others.

Types of medication Error are as follows:

<table>
<thead>
<tr>
<th>No.</th>
<th>Types of Medication Error</th>
<th>Definition</th>
</tr>
</thead>
</table>
| 1.  | Prescribing errors                | • Incorrect drug selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors)  
     |                                   | • Incorrect dose, dosage form, quantity, route, concentration, rate of administration, or instructions for use of a drug product ordered or authorized by physician (or other legitimate prescriber)  
<pre><code> |                                   | • Illegible prescriptions or medication orders that lead to errors that reach the patient |
</code></pre>
<p>| 2.  | Omission error                    | The failure to administer an ordered dose to a patient before the next scheduled dose |
| 3.  | Wrong time error                  | Administration of medication outside a predefined time interval from its scheduled administration time |
| 4.  | Unauthorized drug error           | Administration to the patient of medication not authorized by a legitimate prescriber for the patient |
| 5.  | Dose error                        | Dispensing/administration to patient of a dose that is &gt; or &lt; than amount ordered by prescriber or administration of multiple doses |
| 6.  | Dosage form error                 | Dispensing or administration to patient of a drug product is in a different dosage form than that ordered by prescriber |
| 7.  | Drug preparation error            | Drug products are incorrectly formulated or manipulated before dispensing or administration to the patient |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Types of Medication Error</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>Deteriorated Drug Error</td>
<td>Drug that has expired or the physical or chemical dosage form integrity has changed is being dispensed or administered to a patient</td>
</tr>
<tr>
<td>9.</td>
<td>Route of Administration Error</td>
<td>Wrong route of administration is being given for the correct drug</td>
</tr>
<tr>
<td>10.</td>
<td>Monitoring error</td>
<td>Failure in reviewing a prescribed regimen for appropriateness and detection of problems or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy</td>
</tr>
<tr>
<td>11.</td>
<td>Compliance error</td>
<td>Inappropriate patient behavior regarding adherence to a prescribed medication regimen</td>
</tr>
<tr>
<td>12.</td>
<td>Other medication error</td>
<td>Any other errors which does not fall into one of these predefined categories</td>
</tr>
</tbody>
</table>

**Why do we care to report a medication error?**

There are many reasons why we should do so. Firstly, we can share the experience on medication errors with other healthcare professional which have the tendency of doing the same error. Apart from that, reporting a medication error will help to disseminate information on medication safety. It will also help to formulate risk reduction strategies which will help in preventing reoccurrences. Last but not least, as healthcare professional, our goal is always to ensure the safety and well being of our patients.

**How do we handle a medication error?**

The first step is by informing our superior who may be a sister or matron in the ward, pharmacist or doctor. If it’s possible, take a prompt remedial action and after that, make a report of the error and include the proof of error as well. To make a report, two types of form must be filled which are the Incident Reporting Form as well as the Medication Error Form. Send both of these forms to Unit Kualiti or the pharmacy.
How to Prevent Medication Error:

1. Tallman lettering may help us in selecting the correct medication with similar names. For example, carBIMazole and carBAMAZepine.
2. Warning labels such as High Alert Medication can help us to be more vigilant.
3. Drugs which Look Alike or Sounds Alike (LASA) should be kept far from each other to prevent us from picking up the wrong drug. For example, Progyluton & Progynova should be kept away from each other to prevent errors from happening.
4. LASA medications must always be updated and reviewed from time to time.
5. The information on LASA must also be disseminated to all healthcare providers. This can be done by distributing posters on LASA to every wards and clinics to ensure that everyone is alert on this issue.

References:
WATCH OUT FOR THESE MEDICATIONS!!!
(LOOK ALIKE SOUND ALIKE)

NOVOMIX (INSULIN ASPART 30% + PROTAMINATED INSULIN ASPART 70%)

ESTROGEN 0.625MG (UP)

ACETYLSALICYLIC ACID 100MG + GLYSINE 45MG (CARDIPRIN)

IRBESARTAN 300MG + HCTZ 12.5MG (CO-APROVE)

DEXAMETHASONE 0.1% EYE DROP (MAXIDEX)

NOVORAPID (INSULIN ASPART)

ESTROGEN 0.3MG (DOWN)

ACETYLSALICYLIC ACID 300MG (ASPIRIN)

IRBESARTAN 300MG (APROVE)

DEXAMETHASONE, NEOMYCIN, POLYMIXIN B EYE OINTMENT
DESMOPRESSIN 0.2 MG  
(MINIRIN)

FERRIC AMMONIUM CITRATE 200 MG/5 ML  
(FAC)

T.FUSIDIC ACID 250 MG

CHLORPHENIRAMINE 2 MG/5 ML SUSPENSION

ESTRADIOL + NORGESTREL  
(PROGYLUTON)

MIST EXPECTORANT STIMULANT

DESMOPRESSIN 0.1 MG  
(MINIRIN)

T.CEFUROXIME 250 MG

PARACETAMOL 120 MG/5 ML SUSPENSION

ESTRADIOL (PROGYNova)
<table>
<thead>
<tr>
<th>Drug Name with Tall Man Letters</th>
<th>Confused with</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorpro<strong>MAZINE</strong></td>
<td>chlorpro<strong>PAMIDE</strong></td>
</tr>
<tr>
<td>DOBUTamine</td>
<td>DOPamine</td>
</tr>
<tr>
<td>ALPRAZolam</td>
<td>LORazepam</td>
</tr>
<tr>
<td>cefTRIAXone</td>
<td>cefTAZidime</td>
</tr>
<tr>
<td>AMPICillin</td>
<td>AMOXycillin</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Trimetazidine <strong>MR</strong> (not available in HPJ)</td>
</tr>
<tr>
<td>isosrbide <strong>DIN</strong>itrate</td>
<td>isosorbide <strong>MONO</strong>itrate (not available in HPJ)</td>
</tr>
<tr>
<td>CLOXAcillin</td>
<td>AMOXycillin</td>
</tr>
<tr>
<td></td>
<td>AMPICillin</td>
</tr>
<tr>
<td>budesonide and <strong>FORMOTEROL</strong> (Symbicort)</td>
<td>budesonide</td>
</tr>
<tr>
<td>No.</td>
<td>Medication Error</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Illegible Handwriting</td>
</tr>
<tr>
<td></td>
<td>On 11&lt;sup&gt;th&lt;/sup&gt; April 2014, a 67 years old male diagnosed with decompensated heart failure, was dispensed with Leflunomide 20mg ON instead of Atorvastatin 20mg ON. On that day, there was a system downtime, which made the doctors unable to prescribe medication in the system, and lead to using of manual prescription. On that busy day, on the prescription, Atorvastatin 20mg ON was interpreted as Arava 20mg ON (brand name of Leflunomide), the medication was filled by a Pharmacist Assistant Trainee, and the error was not noticed during counterchecking. This error was noticed when patient was admitted to the ward on May 2014.</td>
</tr>
<tr>
<td>2</td>
<td>Wrong Strength (Trimetazidine Tablet)</td>
</tr>
<tr>
<td></td>
<td>One of patient’s home medication was trimetazidine MR 35mg BD. Unfortunately, the only available strength of trimetazidine that is available in Hospital Putrajaya is trimetazidine 20mg (dose: 20mg TDS). When he was warded in Hospital Putrajaya, the patient was prescribed with trimetazidine 35mg BD, and dispensed (without counterchecking) with trimetazidine 20mg tablet, with the instruction of taking 1¾ tablet two times a day.</td>
</tr>
<tr>
<td>No.</td>
<td>Medication Error</td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
</tr>
</tbody>
</table>
| 3.  | Wrong Strength (Leuprolide Injection) | i) Dissemination of information regarding new drug in Hospital Putrajaya, new item arrival, reasons of new code and batch changes.  
ii) Different strengths of Leuprolide Injections should be located further apart.  
iii) Drug labels should be placed on the medication, but must not cover the name and strength of the medication (eg. At the back of the box)  
iv) For administration process, second checker must counterchecked and reinforce 7R (right drug, right dose, right route, right patient, right time, right documentation, and right to refuse) basic administration procedure. |

In the month of June 2014, there were 2 medication errors involving Leuprolide injection. The patients were intended for **leuprolide 3.75mg injection** monthly, however they **leuprolide 11.25mg injection** was dispensed and administered to the patient. These incidents occurred because of leuprolide 11.25mg was a new drug in Hospital Putrajaya, which was intended to be used only after leuprolide 3.75mg finish stock and discontinued from Hospital Putrajaya. During stock receiving, filling, counterchecking, dispensing and administration, it was not noticed that there was a new strength of leuprolide available.

In conclusion, counterchecking must be emphasized every time before dispensing. Any discrepancies must be clarified and must not be assumed or guess. If there are any questions, the prescriber must be contacted prior to dispensing. All healthcare professionals, be it pharmacists, medical officer and nurses, are responsible in ensuring patient received right drug, right dose, at the right time.

Reference: