Devising outlier-based alerts for medication orders

Gouri Prakash1
CitiusTech Inc, Mumbai, India

Abstract. Drugs are chemical substances, which can, on consumption and under certain conditions, be toxic and cause Adverse Drug Reactions (ADRs) in patients. This paper puts forth the proposition of generating a systemic alert to a clinician, at the time of placing a medication order for a patient, when the number of ADRs associated with the selected medication is significantly different from the number of ADRs associated with other drugs approved for the same therapeutic area.

Keywords. Drug-Related Side Effects and Adverse Reactions, Medical Order Entry Systems, medication alert system, Drug safety

Introduction

Europe has always been at the forefront of harmonization of regulations that allow diseased populations faster and cheaper access to approved drugs. The European Medicines Agency (EMA), which came into effect in 1995, is vested with the right to approve the grant of centralized authorization, to drug manufacturers, for the sale of drugs throughout European Union and the European Economic Areas (EEA) countries. It is a regulatory requirement in Europe, that the Marketing Authorization Holder (MAH), or drug manufacturer, publish a list of Adverse Drug Reactions (ADRs) associated with the approved drug, in a document called the Summary of Product Characteristics (SPC). The SPC is available to the public, for interpretation of therapeutic indications supported by the approved drug. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTiun (PROTECT) was formed in 2009; its activities are funded by the Innovative Medicines Initiative, a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The PROTECT network comprises of public and private partners, coordinated by the EMA, to strengthen the monitoring of the benefit-risk quotient of medicines available in Europe. One of the initiatives of PROTECT, has been to compile ADRs found in section 4.8 of the SPC. This compilation of ADRs is referred to as the PROTECT ADR database [1].

Computerized Provider Order Entry systems (CPOEs) and e-prescription systems enable clinicians to place orders for medications, electronically, wherein the clinician selects a medication, from a pre-defined list, and the order is routed electronically to the pharmacy to action the prescription. Certain CPOEs have built-in clinical decision support rules that alerts clinicians to the potential risks of prescribing the selected

1 Corresponding Author: Sr. Manager, Quality Assurance, CitiusTech, 41/2, Saki Vihar Lake Rd, Andheri(East), Mumbai – 400072, India; Email: gouri.prakash@citustech.com
medication for the patient at the time of order entry [2, 3]. Contemporary practice on alert generation, at the point of entry for medication orders - as evinced by the latest edition of a CPOE Evaluation Tool, put forth by Leapfrog [4], a US-based, Patient Safety Organization, (PSO) - places emphasis on (i) the interaction of drugs with other substances (ii) the administration of drug in its approved form (iii) contraindications based on patient characteristics such as age, pregnancy, so on and so forth.

This paper discusses a new category of alerts. The information provided in section 4.8 of the SPC, and subsequently collated in the PROTECT ADR database, can be utilized to identify those drugs, for which the number of associated ADRs is unusual, when compared to the number of ADRs associated with other drugs approved for the same therapeutic indication. Outliers of interest, for the purposes of this paper, are drugs associated with an unusually high or an unusually low number of ADRs, relative to other drugs developed for the same therapeutic indication. The central premise of this paper is that the selection of an outlier, as the medication of choice for a patient, by a clinician, should be the basis for generating the alert.

1. Methods

The PROTECT ADR database, containing ADR profiles of drugs, in authorized status, as of June 30th, 2013, was downloaded from the PROTECT web portal [1]. For each ADR record in the database, pertinent information was extracted, which included – the name of the branded medicine, the substance name, (Active Principal Ingredient (API) in the drug), the name of the ADR and the causality information which indicated the certainty with which the ADR was associated with the approved drug and whether the ADR was uncovered during clinical trials or during post-marketing surveillance studies.

There were 48,611 ADR records in the database. For 516 of these records, the causal relationship between the drug and the ADR was suspected but not established – these records were removed from the dataset. Drugs approved for multiple indications were de-scoped from the analysis, as the ADR counts for these drugs takes into account multiple therapeutic areas. Drugs, for which the “authorized” status was annulled by the EMA, after June 30th 2013, were also de-scoped.

The processed dataset was used as the basis for computing the number of ADRs associated with each branded medicine, in centralized authorized status as of Feb 4th 2015. The therapeutic indication supported by each drug was identified based on the information available on the European medicines web portal [5]. Test for the presence of outliers was conducted amongst drugs approved for a single therapeutic area.

The effectiveness of an outlier detection test depends on the number of data points (number of approved drugs) available per therapeutic area. The methods employed, make no assumptions about the underlying distribution of data points. Tukey’s boxplot [7] was used to detect the presence of outliers for therapeutic areas for which the EMA had approved at least 30 drugs – there were only 3 of these - diabetes, HIV and hypertension. For all other therapeutic areas, the number of drugs approved for a single therapeutic area, was less than 15. For therapeutic areas where the number of drugs was between 5 and 15, the adjusted boxplot [8] was used as Tukey’s boxplot is not suitable for detecting outliers when the number of data points is less than 30 [9]. In practice, boxplots are employed, when there are more than 5 observations in the dataset. Hampel’s method [10] was employed for detecting outliers, where the number of drugs per approved therapeutic area was 3, 4 and 5.
2. Outlier analysis

The side-by-side boxplot, in Figure 1 shows the distribution of the number of ADRs per drug, for therapeutic areas with more than 30 approved drugs - diabetes, HIV and hypertension. Figure 1 shows, that although EMA has approved more than 50 drugs for diabetes, the number of ADRs for approved drugs has an upper bound of 50. The relatively higher median for HIV and hypertension indicates a higher risk tolerance for drugs developed for these pathological conditions.

Figure 1. Number of ADRs per drug for therapeutic areas with more than 30 approved drugs

To test for presence of outliers for therapeutic areas, with fewer than 15 approved drugs, a stratified random sample was created, where each stratum comprised of therapeutic areas with k number of approved drugs. The values for k were as follows:

\[ k = \{3, 4, 5, 6, 7, 9, 10, 11, 12\} \]

From each stratum, a therapeutic area was randomly selected and the outlier detection test was applied to the set of drugs approved for that therapeutic area. Table 1 shows the therapeutic areas for which the test for outlier drugs was conducted.

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th># of drugs</th>
<th># of outliers</th>
<th># of ADRs per outlier</th>
<th>Outlier detection test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedemas, hereditary</td>
<td>3</td>
<td>0</td>
<td>-</td>
<td>Hampel's</td>
</tr>
<tr>
<td>Prostatic, neoplasm</td>
<td>4</td>
<td>0</td>
<td>-</td>
<td>Hampel's</td>
</tr>
<tr>
<td>Arthritis Rheumatoid</td>
<td>5</td>
<td>2</td>
<td>26 and 192</td>
<td>Hampel's</td>
</tr>
<tr>
<td>Breast neoplasm</td>
<td>6</td>
<td>0</td>
<td>-</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>7</td>
<td>1</td>
<td>46</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>9</td>
<td>1</td>
<td>26</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>10</td>
<td>0</td>
<td>-</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>COPD</td>
<td>11</td>
<td>0</td>
<td>-</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12</td>
<td>1</td>
<td>144</td>
<td>Adj. boxplot</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>0</td>
<td>-</td>
<td>Tukey’s boxplot</td>
</tr>
<tr>
<td>HIV Infections</td>
<td>31</td>
<td>2</td>
<td>177 and 198</td>
<td>Tukey’s boxplot</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55</td>
<td>1</td>
<td>58</td>
<td>Tukey’s boxplot</td>
</tr>
</tbody>
</table>

From the above data, it was inferred that the presence of outliers in a set of drugs approved for a single therapeutic indication is statistically significant (p<0.01).
3. Alert workflow

The ensemble of structural components and actors of the alert workflow is given in Figure 2. When a clinician selects a medication for prescription, an alert rules engine checks to see if the number of ADRs for the selected medication, renders it to be an outlier, with respect to average number of ADRs associated with other drugs approved for the same indication and accordingly generate an alert to the clinician at the point of entry for medication orders.

It is possible that a drug associated with an unusually high number of ADRs, is also, comparatively more effective, and the clinician would prefer to prescribe such a drug, regardless of the relative number of ADRs associated with the drug. Hence, the recommendation here is to generate a “soft” alert as opposed to a “hard” alert. A soft alert [11] permits the clinician to override the alert. A hard alert prevents the clinician from placing the order for which the alert was generated. A clinician, when faced with the soft alert has to decide whether the risks for prescribing the medication, flagged by the system as an outlier, are acceptable, given the efficacy of the approved drug. The clinician can either override the alert or accept it and select another medication. The purpose of generating the alert is to provide clinicians with pertinent data, at the point of entry of medication orders and enable them to make an informed clinical decision.

The SPC of approved drugs is continually updated by drug manufacturers, as new and relevant information becomes available. The PROTECT ADR database is updated once, annually, and as such renders a snapshot in-time-view of the ADR profiles for approved drugs. However, the EMA endeavours to maintain up-to-date information on the web medicines portal. Hence, to account for the disparity in the volatility of data
and to ensure accuracy, an alternative, to using the PROTECT ADR database is for the solution provider to maintain an up-to-date ADR profile for approved drugs by sourcing the information directly from the latest version of the SPC documents and to integrate this information at the point of entry for medication orders.

4. Discussion

The concept presented in this paper is important from a patient safety and quality of care perspective. Every drug is capable of producing ADRs in humans on consumption [12, 13]. This paper proposes a solution that designates a drug as an outlier based on “peer” evaluation of the drug with respect to its ADR profile. That the drug has garnered approval from regulatory authorities should not pre-empt this evaluation. A drug which is contemporarily and habitually, prescribed in practice, may become an outlier in the future, when the number of associated ADRs is unusual, compared to other drugs prescribed for the same pathological condition, given the dynamic safety profile of the drug, post the approval of a drug for centralized authorization status.

While this paper lays emphasis on generating alerts based on prescribing “outliers”, the detection of which can be conducted when there are at least 3 drugs for the same therapeutic indication, in the case where there are only 2 drugs approved for the same therapeutic indication, computing the distance between the ADR counts, in terms of the drug approved with the lower number of ADRs, can provide qualitative, if not statistically supported, insight into the implications of prescribing the drug with the substantially higher number of ADRs.

References