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Objectives: Pharmacometric (PM) analysis is critical for understanding the dose-exposure-response relationship throughout drug development. We surveyed PM analyses and their impact on the approval and labelling of all New Molecular Entities (NMEs) in oncology that were approved by FDA from 2005 to 2015. The objectives are to systematically present an overview of the PM analysis impacting the approval and labeling of NMEs approved for oncology use from 2005 to 2015.

Methods: PM analysis information was obtained from the “Clinical Pharmacology & Biopharmaceutics Reviews” of each NME (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). Results from both the FDA and Sponsor were included. Impact was assigned to one of four categories based on any reported PM details and supported dose adjustments. Dosage information was collected from the approved and revised labels. The impact was compared over two time periods, 2005-2009 and 2010-2015.

Results: From 2005 to 2015, FDA approved 69 NMEs in oncology consisting of 51 small and 18 large molecule drugs. Overall, a large increase in approved drugs was seen between the two time periods (Table 1). A shift was observed in the use of PM analysis (66% vs. 82 %) and more importantly in the impact on the labelling (22% vs. 67%). The impact on the label for large molecules (2010-2015) mirrored that for small molecules. PM analysis supported dose adjustment without support of a dedicated study (renally impaired) in only one label.

Table 1: Summary of pharmacometrics impact on oncology NME approvals and labels, 2005-2015

<table>
<thead>
<tr>
<th></th>
<th>Small molecules (N=51)</th>
<th>Large molecules (N=18)</th>
<th>All (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>2005 - 2009</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2010* - 2015</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Categories: A) No PM performed, B) PM performed but no mention in the label, C) PM performed and mentioned in the label – no dose adjustment, D) PM performed and mentioned in the label – dose adjustment supported.

*Only 2 drugs were approved in 2010.

Conclusions: Pharmacometric analysis is playing an increasingly important role in supporting dose labeling for oncology drugs. It now impacts over 60% of recently approved small and large molecule therapeutics, a level on par with that of non-oncology drugs reviewed earlier. Even when no dose adjustment is recommended, PM efforts play a strong and expanding supportive role in that determination.

Reference: