Amount of Radioactivity and Estimated Effective Dose Equivalents for Research Subjects Given $^{14}$C/$^{3}$H Drugs in Absorption, Metabolism and Excretion Studies


Background

The Food and Drug Administration (FDA) and Nuclear Regulatory Commission (NRC) jointly regulate absorption, metabolism, and excretion (AME) studies in the US. The AME Sponsor (Pharmaceutical Company) must solicit either direct FDA approval (via filing or amending their drug’s IND) or get indirect FDA approval via a Radioactive Drug Research Committee (RDRC). RDRCs are FDA-approved and NRC-regulated in accordance with 21 CFR 361.1; this is also the only FDA-regulation that provides AME Sponsors a reference for what radioactive dose could be justified in the Sponsor’s IND submission as “safe” whole body (WB) and individual tissue radiation exposures to research subjects. WB exposure, presented herein as effective dose equivalents (EDEs), can be estimated from appropriate (pigmented) animal radiation exposure data for the same $^{14}$C- or $^{3}$H drug planned to be given to the research subjects. For 200 $^{14}$C-drug doses, the associated WB EDE and tissue exposure estimates were analyzed to determine if evaluating pigmented tissue exposures would affect AME Sponsor’s decision on how much $^{14}$C/H-radioactivity could be given to the research subjects.

Methods

In each AME study, for the amount of $^{14}$C/H-drug to be dosed to the human subjects, the WB EDE was estimated using International Commission on Radiological Protection (ICRP) Method 30 weighting factors where the tissue exposure data in whole or in part from pigmented animals was used to estimate the corresponding human tissue exposures.

Top of Table 1 presents the various weighting factors for 3 industry-acceptable ICRP Publications/Methods and a worst-case example for a 100 µCi $^{14}$C-drug dose using either pigmented or albino rat data. Bottom of Table 1 presents maximum radiation exposure recommendations for radiation workers, research subjects, and members of the public.

ICRP has twice revised their methods and recommendations, whereas the NRC/CFD regulations listed in Table 1 have remained consistent with the original 1977/79 ICRP Publications 26/30.

For research subjects, only the FDA has set limits for the maximum radiation exposures to 3 critical tissues/organs (gonads, bone marrow, and lens of the eye).

This FDA requirement to evaluate the lens of the eye exposures necessitates that RDRCs as well as Sponsors in their IND filings derive human dosimetry estimates based on pigmented animal data instead of only using albino animal data.

Data was summarized for 200 $^{14}$C/H-drug doses given at the Covance-Madison Clinical Research Unit (CRU) between April 2001 and May 2013.

Each AME study protocol was approved by the Covance-Madison Radiation Safety Committee (RSC) and by an independent Institutional Review Board (IRB).

Each subject signed an IRB-approved informed consent prior to AME study participation and consent included information (provided by RSC) on WB radiation exposure estimates associated with the planned $^{14}$C/H-dose.

The $^{14}$C- or $^{3}$H-dose were administrated to human subjects under the drug’s IND filed with the FDA (for 199 of the 200 $^{14}$C/H-drug doses) or under approval by the Covance-Madison RDRC.

Since an AME study conducted under an existing IND does not require FDA pre-approval of the radioactive dose amount given to the research subjects, the Covance RSC uses the maximum exposure limits in 21 CFR 361.1 to guide the RSC in what the FDA might approve for the AME Sponsor as a “safe radioactive dose.”

Covance-Madison CRU’s authority to dose $^{14}$C- or $^{3}$H-drugs was granted via a medical-use radioactive materials license initially issued by the NRC and renewed in 2003 by the NRC-delegated WI Agreement State agency.

Table 1. Weighting Factors and Recommended Maximum Radiation Exposures in ICRP Publications and in US NRC/FDA Regulations

<table>
<thead>
<tr>
<th>Organ or Tissue</th>
<th>Recommended Max</th>
<th>ICRP 1991</th>
<th>ICRP 1977/79</th>
<th>FDA 21 CFR 361.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Lens</td>
<td>3,000 mrem per study</td>
<td>3,000 mrem per study</td>
<td>3,000 mrem per study</td>
<td>3,000 mrem per study</td>
</tr>
<tr>
<td>Skin</td>
<td>50,000 mrem per year</td>
<td>50,000 mrem per year</td>
<td>50,000 mrem per year</td>
<td>50,000 mrem per year</td>
</tr>
</tbody>
</table>

Table 2. Summary of Radioactive Amount Dosed and Estimated Radiation Exposures

<table>
<thead>
<tr>
<th>Organ or Tissue</th>
<th>Linear Regression</th>
<th>Linear Regression</th>
<th>Linear Regression</th>
<th>1991 Recommendations: ICRP Publications 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Lens Radiation Exposure (mrem)/µCi Dosed</td>
<td>0.0033 mrem/µCi</td>
<td>0.0033 mrem/µCi</td>
<td>0.0033 mrem/µCi</td>
<td>NRC: 10 CFR Part20</td>
</tr>
<tr>
<td>Uveal Tract Radiation Exposure (mrem)/µCi Dosed</td>
<td>0.0033 mrem/µCi</td>
<td>0.0033 mrem/µCi</td>
<td>0.0033 mrem/µCi</td>
<td>FDA: 21 CFR 361.1</td>
</tr>
</tbody>
</table>

Table 2 confirms that the US industry-standard/most common $^{14}$C-drug dose amount was 100 µCi (dosed 72% of the time).

The highest $^{14}$C-drug dose given was a 2500 µCi dose (with an estimated WB EDE of 9 mrem—reason for such a low WB EDE was due to this orally dosed drug being only 2% absorbed).

The highest $^{3}$H-drug dose given was a 786 µCi dose (with an estimated WB EDE of 2 mrem).

Global regulatory agencies require Sponsors to evaluate the presence of unique or disproportionate “metabolites in safety testing” (MIST) as a result, $^{14}$C- and $^{3}$H-drug doses $>$100 µCi have become more common: observed in about 25% of the $^{14}$C/H-drug exposures (Table 2).

For research subjects, 21 CFR 361.1 lists the maximum radiation exposure limits allowed to be approved by RDRCs and typically used by Sponsors in their $^{14}$C/H-drug IND filings/aminations (Table 1).

For research subjects, the ICRP and European regulatory agencies have no published radiation exposure limits for critical tissues/organs.

For research subjects, 21 CFR 361.1 does list maximum individual tissue/organs limits: 3,000 mrem/study limit for 3 critical tissues/organs (gonads, bone marrow, and lens of the eye) and 5000 mrem/study limit for any other tissue/organ (Table 1).

The highest WB EDE was 17.433 mrem/µCi for a $^{14}$C-drug dose (Table 1, 4th column and Figures 1 and 2).

The highest WB EDE was 0.336 mrem/µCi for a $^{3}$H-drug dose (Table 1, 4th column and Figures 1 and 2).

The last row in Table 2 highlights the importance of including radiation exposures for pigmented tissues: when a single tissue disproportionately influences (i.e., field the WB EDE, nearly the time of 48%) it was caused by a pigmented tissue (either lens of the eye or eye uveal tract).

If the US AME Sponsor’s maximum standard dose of 100 µCi was arbitrarily chosen by an AME Sponsor, based on the data summarized in Table 1, $^{14}$C-drug radiation exposure limits in 21 CFR 361.1 would have been exceeded in 4 instances (i.e., 2% of the time) once involving excessively high radiation exposures to the lens of the eye and tissue to eye uveal tract, with the ultimate safety concern being elevated/unacceptable risk for cataract formation in the research subject.

Conclusions

For 4 of the 195 $^{14}$C-drug doses analyzed, if an AME Sponsor were to use the maximum amount of $^{14}$C-radioactivity (i.e., 100 µCi), the maximum radiation exposure limits in 21 CFR 361.1 for individual tissues/organs would have been exceeded due to excessively high radiation exposure to a pigmented tissue.

Recognizing that there are cases in which the industry standard of ≤100 µCi exceed the dose exposure considered safe for radiation workers, Covance RSC highly recommends that estimated human radiation exposures to research subjects from $^{14}$C- or $^{3}$H-drugs should be derived from pigmented animal data.

This Covance RSC recommendation is especially important when one realizes the radiation exposures being demonstrably influenced (>10-fold) the WB EDE, nearly the time of 48% it was caused by a pigmented tissue (either lens of the eye or eye uveal tract).

Using $^{14}$C-drugs $>$100 µCi becomes increasingly more common and may be useful to address AME study objectives, such as the MIST regulatory requirement.