Regulatory Considerations for Alpha-emitting Drug Products

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Radiopharmaceuticals are listed on Schedule C to the *Canadian Food and Drugs Act* and are specifically regulated under Part C, Division 3, of the *Food and Drug Regulations*. Divisions 1 (DINs), 1A (Establishment Licensing), 2 (GMPs), 5 (Clinical Trials) and 8 (New drugs) also apply.

Alpha-emitting radiopharmaceuticals fall within this regulatory framework;
- The usual chemistry, manufacturing and controls (CMC) information is expected in support of a CTA or NDS.
- However, their properties can lead to some product-type-specific expectations regarding data for evaluation.
Regulatory Experience

- At Health Canada: One approved product $^{223}$RaCl$_2$; and one approved CTA involving Ab-conjugated with $^{225}$Ac.

- More broadly: Alpha-emitting radionuclides that have been investigated in both pre-clinical and clinical studies are listed below:

<table>
<thead>
<tr>
<th>Isotopes</th>
<th>Energy (MeV)</th>
<th>t1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{211}$At</td>
<td>5.87</td>
<td>7.2 hours</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>5.94</td>
<td>10 days</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>5.87</td>
<td>45.6 minutes</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>5.71</td>
<td>11.4 days</td>
</tr>
<tr>
<td>$^{224}$Ra</td>
<td>5.69</td>
<td>3.63 days</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>6.05</td>
<td>60.6 minutes</td>
</tr>
</tbody>
</table>
CMC information

- In addition to the method of production of the parent radionuclide and the rationale for the radionuclide selection, the following information should be provided:
  - Consideration should be given to all the daughters produced, their half-life and biodistribution.
  - Recoil energy of each daughter and ability to remain attached to the chelate.
  - Radionuclidic purity should be provided.

- Information on the selection of the targeting moiety:
  - Receptors with or without mediated endocytosis.
CMC information

- Choice of labelling method: electrophilic substitution through tin precursor or chelation.
- Information on the manufacturing process and in-process controls.
- Selection of solvents, buffers and radioprotectant to minimize radiolysis.
- Stability in serum *in vitro*.
- Dosimetry.
- Information on the manufacturing facility.
A major distinguishing feature of Alpha-emitters

- Alpha emitters are highly energetic therapeutic radionuclides. Therefore, the toxicity should be minimized and the steps taken to reduce the toxicity should be highlighted in the regulatory submission.
Strategies being considered to minimize damage to healthy tissues

- Pre-targeting, where an antibody coupled with an avidin/streptavidin moiety is injected, followed by injection of a small molecule such as a biotin labeled with an alpha-emitting radionuclide, allowing fast clearance of the radioactive small molecule.

- Encapsulation of the alpha-emitting radionuclide into a nanocarrier to retain the recoil daughters.

AND

- Brachytherapy with wire sources impregnated with the radionuclide for local administration (would be regulated as a Medical Device).
Available Guidelines and Templates

- The following guidance documents are available:
  - Radiopharmaceuticals, Kit and Generators: Submission Information for Schedule C Drugs (guidance release targeted for summer 2019)
  - Annexes to the GMP Guidelines (GUI0001) for radiopharmaceuticals (GUI0071 and GUI0026)
  - ICH-CTD format (M4Q(R1))

- Submission Templates:
  - QIS-R, CPID-R (available from Office of Regulatory Affairs, BGTD)