Table 10: Breakthrough Therapies

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<th>Session 1</th>
<th>Session 2</th>
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**SCOPE:**
Breakthrough designation is an expedited drug development pathway for drugs intended to treat a serious or life-threatening condition in an area of unmet medical need and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on a clinically significant endpoint(s). Breakthrough designation allows creative ways to compress overall timeline to reach approval without impacting quality and safety of the product. Most requests for breakthrough designation are not granted, and of those products for which BT status is granted, most breakthrough products are not approved. For example, in fiscal year 2018, CDER received 139 breakthrough therapy designation requests and granted 51 of those while CBER received 21 requests and granted 7. Of all products that were granted BT designation, CDER has approved 49% and CBER has approved 15%.

In this round table, we will discuss how breakthrough status impacts CMC development, and how CMC issues may impact approval of a designated breakthrough product.

**QUESTIONS FOR DISCUSSION:**
1. How does the approach to product development change with breakthrough designation? What is different about RMAT designation?
2. What are the main CMC obstacles to the timely approval of a breakthrough product?
3. What are some points to consider for analytical method development for breakthrough products?
4. How does FDA expedite product approval through the breakthrough pathway?
5. What CMC strategies have promoted successful approval of a breakthrough product?

**DISCUSSION NOTES:**

**Day 1:**
1. **Changes in Approach to Product Development with BT designation:**
   a. Were not allowed to submit DS first for rolling review, had to submit whole Module 3
   b. Utilized development runs to generate important supportive stability data
   c. Few lots generated therefore focus on broad specifications with commitment to re-evaluate post-approval (number of lots post-approval in re-evaluation dependent on number of lots created in years time)
2. **Main CMC obstacles to timely approval for BT Products:**
   a. Getting all validation completed, in some cases needed to outsource to keep on track
   b. Utilizing development runs to generate number of lots used for stability
   c. Comparability assessments to cover process/site changes with 1 lot put on stability

3. **PTC for analytical method development for BT Products:**
   a. Include stability degradation to predict impurities
   b. Validate out routine testing where possible such as with Host Cell Proteins
   c. Save sample form all clinical batches, in an event of method change, retest all clinical lots

4. **Expedited Product Approval Process:**
   a. Argentina has 8 month process for rare diseases but also special program for individual patients that can be approved in 15 days
   b. Experience that FDA and EU had consistent requirements and similar questions

5. **CMC Strategies that were Successful for BT Products:**
   a. Same data set but with slight less detail for less mature health authorities
   b. Used 3 PPQ lots to demonstrate control strategy
   c. Used full CMC package not paired down, did not postpone to commitment. Some information allowed to be submitted during review process like stability.
   d. Went overboard in number of lots used for stability to avoid global questions, could have done with just one. Included end-to-end worse case process variability in stability lots(experience with TGA sometimes requesting).
   e. Significant process change was addressed by including a side arm in the phase 2 to show comparability