Medtronic Activa® Dystonia Therapy

Humanitarian Device Exemption (HDE) H020007

Ann H. Costello Ph.D., D.M.D.

Pediatric Advisory Committee
April 21, 2014
Presentation Outline

Device Description, Regulatory History & Pre-Market Clinical Data:
   Ann H. Costello Ph.D., D.M.D.

Postmarket Medical Device Reporting & Systematic Literature Review:
   Nicholas Werner B.E.
   Nathan S. Ivey Ph.D.
Indication for Use

The Medtronic Activa® Dystonia Therapy is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPI) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.
Device Description
Regulatory History

- HDE Approval: April 15, 2003
- Approval of Request for Determination under FDASIA Section 613(b): January 16, 2013
Overview of Dystonia

• Hyperkinetic movement disorder characterized by sustained twisting and posturing movements, which may affect single or multiple body areas.
• Classified by age of onset, affected body area and etiology.
• Alternative treatment includes anticholinergics, (Artane and Cogentin) and botulinum toxin
Link to Video Clip
Pre-Market Clinical Data

• Approval based on 34 published articles of device use in pediatric and adult patients with dystonia

• Articles consisted of:
  – Retrospective, single institution, unblinded case series
  – Various classification and rating scales
HDE Patient Cohort (n=201)

Females: 41%
Males: 28%
Not specified: 30%

<table>
<thead>
<tr>
<th>Age Classification</th>
<th>N</th>
<th>Average Age (yrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric (0-12 yrs.)*</td>
<td>21</td>
<td>8.8</td>
</tr>
<tr>
<td>Adolescent (13-17 yrs)</td>
<td>18</td>
<td>14.8</td>
</tr>
<tr>
<td>≥ 18 yrs.</td>
<td>53</td>
<td>39.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>109</td>
<td>-</td>
</tr>
</tbody>
</table>

*81% of pediatric population (N=21) > age 7

FDA guidance published in 2004: “Premarket Assessment of Pediatric Medical Devices”

<table>
<thead>
<tr>
<th>Pediatric Subgroup</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Birth to 1 mo</td>
</tr>
<tr>
<td>Infant</td>
<td>&gt; 1 mo to 2 yrs</td>
</tr>
<tr>
<td>Child</td>
<td>&gt; 2 yrs to 12 yrs</td>
</tr>
<tr>
<td>Adolescent</td>
<td>&gt; 12 yrs to 21 yrs</td>
</tr>
</tbody>
</table>
## Dystonia Type (n=201)

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>% (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>131</td>
<td>65.2</td>
</tr>
<tr>
<td>Cervical</td>
<td>17</td>
<td>8.5</td>
</tr>
<tr>
<td>Segmental</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Hemidystonia</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Multifocal</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Cervical (and truncal)</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Focal</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Unspecified</td>
<td>34</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Dystonia is classified by age on onset, affected body area and etiology. Early onset: Age < 26 years; begins with symptoms in the limbs, typically the leg, and spreads to other body areas to become generalized in over 50 percent of patients.
Follow-up

• Range: 0.7 to 132 mos. (avg. 12.1 mos)

• Data are available on 191 of 201 subjects
  – > 50% of dystonic patients had > 3 months of follow-up

• Target:
  – GPi: bilateral 71.2%, unilateral 6.8%
  – STN: bilateral 7.3%
Burke-Fahn- Marsden Dystonia Rating Scale (BFM)

• Used to assess probable benefit; appropriate for generalized, segmental, or focal dystonia, or may be focused on one body area, such as cervical dystonia.

• Two sections:
  – movement scale based on the neurological examination
  – disability scale based on the patient’s opinion of their disability in activities of daily living.

• Total combined score range from 0 to 120
Probable Benefit

• Based on 3 papers with ≥ 10 subjects
• Coubes: 19 subjects with generalized dystonia positive for the DYT1 mutation
  – Clinical score improvement of 71% following one year of therapy
• Vidaihet: 14 subjects with primary generalized dystonia
  – Clinical scores decreased from 56 ± 21 preop to 26 ± 16 postop (at least 6 mos FU)
• Broggi: 10 primary dystonia patients
  – Clinical improvement between 27% and 88% in 8 subjects (up to 6 mos FU)
Probable Benefit in Children

- 8 papers discuss benefit in pediatric subjects
  - Coubes: 20 dystonic children (≤12 yrs) and 14 adolescents (13 to 17 yrs)
- BFM scores in subjects with generalized dystonia positive for the DYT1 mutation were:

<table>
<thead>
<tr>
<th>Time</th>
<th>BFM Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>61 ± 23</td>
</tr>
<tr>
<td>3 Mos.</td>
<td>21 ± 21</td>
</tr>
<tr>
<td>6 Mos.</td>
<td>11 ± 11</td>
</tr>
<tr>
<td>12 Mos.</td>
<td>14 ± 17</td>
</tr>
</tbody>
</table>
Safety (n=201)

- Hemiplegia/Hemiparesis
- Worsening of Motor Impairment (dysphagia)
- Sensory Impairment
- Speech/Language
- Subcutaneous Hemorrhage/Seroma
- Cerebral Spinal Fluid Abnormality
- Infection
- Erosion
- Lead fractures, Hardware Breakage, IPG Failure
- Déjà vu corrected by surgically revised lead placement
- Irritating cough with stimulation ON
Safety Analysis

Risks associated with DBS for dystonia appeared similar to risks associated with stereotactic surgery and DBS implant for Parkinson’s disease and essential tremor
Pediatric Specific Safety Concerns

• Lead breakage related to elongation of trunk
• Lead migration due to head growth
• Device issues due to child’s play/sports activities

Mitigating factors

• Monitor lead for sufficient strain relief
• Limit to age > 7 years to account for head growth
• Consider extension replacement during other elective procedures
• Lead reprogramming
Safety and Probable Benefit

- The collective evidence of the papers demonstrated a reasonable assurance of probable benefit for the indicated patient population.
  - Data on 39 pediatric subjects was reviewed and demonstrated probable benefit in this population.
- The safety profile was similar to that of approved DBS populations.
  - Mitigating factors addressed pediatric specific safety concerns.
Safety and Probable Benefit

● Chronic intractable dystonia is very disabling and may progress to a life-threatening stage
● Limited treatment options exist for subjects with dystonia
● Prior to HDE approval, ablative surgery (an irreversible, destructive procedure) was typically the last option for drug refractory dystonia
Annual Distribution Number (ADN)

- HUD was approved with ADN = 4000.
- 2,090 dystonia therapy systems were distributed in 2013 in US
References


2014 PAC Panel Meeting
Medtronic’s
Activa® Neurostimulator for Dystonia Treatment
H020007

Nicholas Werner
Biomedical Engineer
Office of Device Evaluation
Center for Devices & Radiological Health
Food and Drug Administration

April 21, 2014
Medical Device Reports (MDR)

Internal CDRH Databases Searched

MDR Search Criteria
  – Premarket Submission Number: H020007
  – Dates: Up to 9/27/13

Search Results: 274 Unique MDRs
Overview of MDRs

**Reporting Country:** (data available in 270 MDRs)
- U.S. 182
- OUS 88

**Patient Gender:** (data available in 204 MDRs)
- Male 99
- Female 105

**Patient Age:**
- Pediatric (≤21) 48
  - Definition has changed since approval
  - Range: 8 – 21 years; Mean 14.73 years
- Adult (>21) 150
- Unknown 76

76% Adult MDRs
## Event Types

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Pediatric</th>
<th>Adult</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Injury</td>
<td>34</td>
<td>102</td>
<td>65</td>
<td>201</td>
</tr>
<tr>
<td>Malfunction</td>
<td>14</td>
<td>46</td>
<td>11</td>
<td>71</td>
</tr>
</tbody>
</table>

1. Serious Injury per regulatory definition (CFR803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

2. A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.
Overview of Pediatric MDRs

Reporting Country: (data available in 46 MDRs)
- U.S. 41
- U.K. 5

Patient Gender: (data available in 46 MDRs)
- Male 23
- Female 23

Event Type:
- Death 0
- Injury 34
- Malfunction 14
# Time to Event (Pediatrics): 0 to 30 Days

<table>
<thead>
<tr>
<th>Reported Problem</th>
<th>Event Type</th>
<th>MDR Count</th>
<th>Injury¹</th>
<th>Malfunction²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 Days Post Implant, n=6</td>
<td>Explant Due to Infection</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Left Facial Weakness / Somnolence</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stroke During Implant</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cerebral Infarction Three Days Post Implant</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lead End Cap Unable to be Removed</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>6</strong></td>
<td><strong>5</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

¹ Serious Injury per regulatory definition (CFR803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

²A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.
## Time to Event (Pediatrics): >30 Days

<table>
<thead>
<tr>
<th>Reported Problem</th>
<th>MDR Count</th>
<th>Injury¹</th>
<th>Malfunction²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater Than 30 Days Post Implant, n=15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of Dystonia</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Explant Due to Infection</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Explant Due to Charging Issue</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Replaced Due to Loss of Therapeutic Effect</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Replaced Due to High Therapy Settings</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Premature Battery Depletion / Return of Symptoms</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unexpected Shock</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Replaced Due to Impedance Issue</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Replaced Due to Broken Leads / Return of Symptoms</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lead Extensions Replaced Due to Fall</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Explant Due to System Positioning</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Explant Due to Charging Time</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>12</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>
## Events of Clinical Interest

<table>
<thead>
<tr>
<th>Event*</th>
<th>Number of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return or Worsening of Symptoms</td>
<td>15</td>
</tr>
<tr>
<td>Explanted</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
</tr>
<tr>
<td>Replaced</td>
<td>7</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>3</td>
</tr>
<tr>
<td>Procedure Related</td>
<td>2</td>
</tr>
<tr>
<td>Battery Issue</td>
<td>1</td>
</tr>
<tr>
<td>Revision Due to Growth</td>
<td>1</td>
</tr>
</tbody>
</table>

* A single MDR may be associated with more than one event.
Events of Clinical Interest

Return or Worsening of Symptoms (n=15)
- Device turned off (ages 12 & 19)
- Battery EOL (age 16)
- High lead impedances (ages 13, 13, 11, & 16)

Explanted (n=9)
- Infection (ages 11, 12, & 21)
- Lead/battery location (ages 13 & 12)
- Charging time length (age 14)
- Device not used (age 19)
- Unknown (age 12)
Events of Clinical Interest

Infection (n=7)
- Staphylococcus Aureus (ages 11 & 12)
  - One treated with IV antibiotics (age 14)
- Lead erosion
- Unknown (ages 10 & 21)
- Unrelated throat infection

Replaced (n=7)
- Loss of therapeutic effect (age 16)
- Short circuit condition (age 19)
- Battery EOL (age 17)
- Unknown
Events of Clinical Interest

Cerebrovascular Accident (CVA) (n=3)

- Small CVA at right caudate head (age 13)
  - Two months after implant

- Cerebral infarction (age 8)
  - Three days post implant
  - Small focus of ischemia/infarction at left caudate head; seen on MRI
  - Possible disruption of small artery

- Stroke and subdural hematoma
  - During implant surgery
  - Patient went into coma (further status unknown)
Events of Clinical Interest

Procedure Related (n=2)
  – Stroke and subdural hematoma (previously covered)
  – Asymptomatic perioperative hemorrhage (age 17)
    • Unknown if intracranial hemorrhage

Battery Issue (n=1)
  – Premature depletion

Revision Due to Growth (n=1)
  – High impedances (age 9)
    • Battery placed in abdomen
    • Longest leads not used
    • Replaced with newer stretch coil extensions
Summary of MDRs

No pediatric death reports

Top patient problem: Return or Worsening of Symptoms
   - Occurred in 31.25% of all pediatric patient MDRs
     • 30.0% of adult patient MDRs
   - Typically resolvable issues (explant or replacement for 3)
   - Addressed in labeling

No new patient problems occurring
Summary of MDRs

Top device problem: High Impedance
- Occurred in 20.83% of all pediatric patient MDRs
  • 15.33% of adult patient MDRs
- Generally associated with symptom return or worsening
- Surgical intervention often required
- Addressed in labeling

No new device problems occurring

Similar MDRs for pediatric and adult populations
- Patient and device problems
- No new or unexpected events
Systematic Literature Review

Inclusion Criteria

• Published after January 1, 2003
• English
• Inclusion of Medtronic DBS device
• Adverse events / safety information
• Indicated for any movement disorder
Systematic Literature Review
Article Retrieval and Selection

Articles reviewed and assessed (n =153)

- Duplicate (n =10)
- No adverse events reported on (n =8)
- Non-English (n =1)
- Non-human (n =31)
- No movement disorder (n =9)
- Non-research article (n =27)
- Unsystematic review (n =4)
- Unrelated topic (n =24)
- No Medtronic device (n =1)
- Article not available (n =2)
- Cohort captured elsewhere (n =1)

Articles included in qualitative synthesis (n=35)
Systematic Literature Review

Study Characteristics

• Thirty-five articles
  – RCTs (n = 1)
  – Observational studies (n = 22)
  – Surveys (n = 2)
  – Case reports (n = 8)
  – Systematic review (n = 1)
  – Case series with systematic review (n = 1)

• Published between 2003 and 2013
• Sample size ranged from 1 to 4,553 subjects.
• US (n = 18) and International (n = 17)
# Pediatric Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range (yrs old)</th>
<th>Sample Size</th>
<th>Length of Follow-Up</th>
<th>IFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghosh</td>
<td>2-15</td>
<td>8</td>
<td>0.5-8 yrs</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Kaminska</td>
<td>4.2-19</td>
<td>25</td>
<td>3-17 mos</td>
<td>Dystonia and Other</td>
</tr>
<tr>
<td>Lumsden</td>
<td>3.3-20</td>
<td>54</td>
<td>&lt;5 yrs</td>
<td>Dystonia and Other</td>
</tr>
</tbody>
</table>
Ghosh et al. (2012)

- US observational study of 8 dystonia pediatrics
- Mean follow-up of 4.7 years
- Mean age 14.1 years
- 37.5% of all patients experienced ≥1 adverse event (AE)
  - Electrode dislocation (n =1), breakage of extension cable (n =1), and infection (n =1)
  - Each yielded a revision.
Kaminska et al. (2012)

- UK observational trial in 25 pediatrics (dystonia n=5); mean follow-up 10 months
- Mean age 11.1 years
- 52% experienced charging problem related AEs
  - Migration of hardware (n=3)
  - Recharger problems (n=2)
  - User problems (n=5)
  - Early seroma (n =4)
  - Erosion over battery site (n =1)
Lumsden et al. (2012)

- UK observational trial in 54 pediatrics (dystonia n =13); follow-up of up to two years
- Mean age 11.1 years
- 100% of patients received a Medtronic device.
- 28% experienced battery failure requiring replacement
  - Mean time to battery failure 24.5±2.9 months (range: 13-39 months)
Adult & Pediatric Populations

• 32 articles had adult and pediatric populations.
• Patients ranged in ages from 4-80 years old.
  – Results not stratified by age
• Sample sizes ranged from 8-4,553 patients.
• 1 randomized controlled trial (RCT) and 31 observational studies
• Indications for use varied across studies.
Volkmann et al. (2012)

- International randomized controlled trial (RCT) of 38 pediatric and adult dystonia patients
- All patients received a Medtronic device
- Mean follow-up of 5 years
- Age range: 14-75 years old
- Adverse events include:
  - infection
  - lead dislodgement/migration
  - lead breakage
  - malfunction
  - cable fracture
  - cervical myelopathy
  - peripheral denervation surgery
  - attempted suicide
  - ineffectiveness
Observational Studies

- Thirty-one articles identified.
- Patients aged from 4-80 years old.
- Sample sizes ranged from 1-4,553.
- Indications for use varied across studies.
  - Each included some movement disorder patients.
Revisions
(14 articles)

<table>
<thead>
<tr>
<th>Revision Type</th>
<th>Overall</th>
<th>End of Battery Life</th>
<th>Other Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of articles</td>
<td>14</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Sample size</td>
<td>1-591</td>
<td>122-420</td>
<td>1-591</td>
</tr>
<tr>
<td>Follow-up (year)</td>
<td>Peri-operative – 8 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>0.7-100</td>
<td>49.5-100**</td>
<td>0.7-100</td>
</tr>
</tbody>
</table>

**Cohort consisted solely of battery replacements.**
### Battery/Power Issues

(9 articles)

<table>
<thead>
<tr>
<th>Issue Type</th>
<th>Overall</th>
<th>Charging issues</th>
<th>Required daily charging</th>
<th>Accidental power down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of articles</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sample size</td>
<td>9-54</td>
<td>1-9</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>2 months – 10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>27.7-100</td>
<td>78-100</td>
<td>45.5</td>
<td>13.6</td>
</tr>
</tbody>
</table>
# Device Failure

(3 articles)

## Failure Mode

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Short Circuits</th>
<th>Disconnected Contacts</th>
<th>Lead Damage</th>
<th>Wire Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of articles</strong></td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>2-591</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Follow-up (years)</strong></td>
<td>1.6 - 2.5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence (%)</strong></td>
<td>0-50</td>
<td>3.7-25</td>
<td>0-1</td>
<td>25-50</td>
<td>0-25</td>
</tr>
</tbody>
</table>
## Additional Adverse Events
(13 articles)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>No. of Articles</th>
<th>Proportion of Patients</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>9</td>
<td>4.5 – 36.8%</td>
<td>Subcutaneous infection, incision site infections, skin erosions, device infections and secondary infections</td>
</tr>
<tr>
<td>Electromagnetic Interference</td>
<td>2</td>
<td>5 – 20%</td>
<td>Results in disabling the device</td>
</tr>
<tr>
<td>Depression /Suicide</td>
<td>2</td>
<td>2 patients</td>
<td>• 63 y.o. female - depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Age not reported – suicidal ideation</td>
</tr>
</tbody>
</table>
Limitations

• Pediatric/adult studies
  – Modest sample sizes (5 studies >100 patients)
  – Mixed age cohorts (not age stratified)
  – Mixed device manufacturers/models within studies
    (4/35 studies included non-Medtronic devices)
Systematic Literature Review: Summary

• The most frequent adverse events included device failure, battery and power issues, infection, and revisions.
Overall FDA Conclusions & Recommendations

- FDA’s Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003.

- Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use.

- FDA will continue routine surveillance including MDR and literature reviews

- FDA will provide focused updated safety and use data to the PAC in 2015.
QUESTION TO THE PAC

Does the Committee agree with FDA’s conclusions and proposed approach?