Reframing How Regulators Use Patient Voice in Decision Making

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2019 RARE Champion of Hope

February 28, 2020
“Patients who live with a disease have a direct stake in the outcome of FDA’s decisions and are in a unique position to contribute to the understanding of their disease.”
Overview

• Evolving Role of Patient Input in Regulatory Decisions
• Emerging Methods
The Evolving Role of the Patient Input in Regulatory Decisions
Patient input can be:

**Product specific**
- FDA Patient Representative Program
- Patient preferences/experiences measured in studies
- Open public hearing at FDA Advisory Committee meeting

**Context-setting**
- Patient-Focused Drug Development meetings
- Listening sessions with FDA
- Qualitative & quantitative methods (e.g., surveys)
- Participating in FDA meetings/workshops
The FDA Approval Decision

- When approving a new drug, FDA must make a determination that the benefits of the drug outweigh the risks.
- It is a scientific determination to evaluate what the benefits and risks are, and how much certainty there is.
- However...
The FDA Approval Decision

- When deciding benefit-risk tradeoffs, this is an inherently subjective value judgment
- Where does FDA calibrate its values on how much risk a patient population should tolerate for a given set of benefits?
Example: Pompe Disease

- FDA recruits patients and caregivers that are also involved in their community (e.g., volunteer with patient group, participate in a support group) as FDA Patient Representatives.

- Serve as consultants during product review (e.g., review protocols at Pre-IND stage, help review study results with internal team).

- Also serve on FDA Advisory Committee meetings for all CDER and CBER committees with a vote.

- Two examples from Myozyme review for Pompe disease:
  1. Understanding study dropouts
  2. Defining clinical meaningfulness
Therapeutic Context in Benefit-Risk Decisions

- To adequately assess benefits and risks, FDA must understand the context in which a potential therapy will be used.
- Two relevant categories of patient experience:
  - The burdens of disease and its impacts on patients’ daily lives.
  - Patients’ perspectives on the adequacy of available therapies.
- This helps FDA understand the types of benefit that matter most to patients.
Questions that Inform the Therapeutic Context

Set 1 - Living with a Condition:

1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?

2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?
   a. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?

3. How have your condition and its symptoms changed over time?
   a. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?

4. What worries you most about your condition?
Questions that Inform the Therapeutic Context (cont.)

Set 2 - Approaches to Treating the Condition:

1. What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, and other therapies including nondrug therapies such as exercise.)
   a. How has your treatment regimen changed over time, and why?

2. How well does your current treatment regimen treat the most significant symptoms of your disease?
   a. How well do these treatments improve your ability to do specific activities that are important to you in your daily life?

3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, restrictions on driving, etc.)

4. What specific things would you look for in an ideal treatment for your condition?
Example: Huntington’s Disease

In September 2015, FDA hosted a PFDD meeting focused on HD

HDSA presented results of a survey that asked about what most burdens patients

Clinicians: slurred speech & chorea

Patients: ability to perform daily activities, including attending school and continuing to work
Therapeutic Context in Benefit-Risk Decisions

**Benefit-Risk Assessment**

- Analysis of Condition
  - Provides regulators with the clinical context for weighing benefits and risks
- Current Treatment Options
- Benefit
- Risk
- Risk Management
  - Incorporates expert judgments based on evaluation of the efficacy and safety data and the expected impact of efforts to reduce and further characterize risks
What about after the first drug is approved?

- Patient experience with approved treatments is critical for FDA understanding shifting burden of disease (if any)

- Example in SMA:
  - Cure SMA held “listening session” with FDA in 2015
  - FDA approved Nusinersen, the first drug for Spinal Muscular Atrophy in 2016, citing its commitment to the SMA community as reason for record-breaking review time
  - Cure SMA held externally-led PFDD in 2017 where patients and caregivers shared experience with that product and remaining unmet medical need
  - This set context for 2019 approval of Zolgensma, a gene therapy for SMA
Clinical outcome assessments (COAs) are measures of how a patient feels or functions.

Can be:
- Measure of performance
- Clinician-reported
- Observer-reported
- Patient-reported

Does not include:
- Survival
- Biomarkers

Used in adequate and well-controlled studies to support approval.
Therapeutic Context in COA Selection & Development

- How do we know what the right concept of interest to measure?
- What opportunities are there to measure a concept of interest in patients’ daily life?
- Do we know what result on a measure is considered clinically meaningful?
Example: EB

“No one knows this diseases better than all of you. What can we do to increase the chances of a trial being able to demonstrate success if the product works? How can we change these trials? What can we do to increase the chances of success?

I think that’s something for all of us to go home and to think about. I will certainly be putting some thought into it”
Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fisher Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Barbara Gould at 301-796-3224 or (CBIR) the Office of Communication, Outreach, and Development at 301-825-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2018
Clinical/Medical

B. Efficacy Endpoints

- Clinical trials should be designed to minimize bias with randomization whenever possible and include an appropriate control to show that the drug provides clinically meaningful improvement in at least one symptom or sign of EB. In appropriate cases, a single adequate and well-controlled trial with supporting evidence may suffice. Examples of meaningful improvement might include significant relief from itching, pain, blister prevention, and wound healing, among others.

- Before commencing clinical trials for EB, it is critically important to reach agreement with FDA about the primary efficacy endpoint(s) and the magnitude of change that will demonstrate clinically meaningful improvement, such as the degree of wound healing.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Patient Organization</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Amyloidosis*</td>
<td>Amyloidosis Research Consortium</td>
<td>November 15, 2015</td>
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<tr>
<td>Mystonic Dystrophy**</td>
<td>Myotonic Dystrophy Foundation</td>
<td>September 15, 2016</td>
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<td>Acute Porphyrinas</td>
<td>American Porphyrina Foundation</td>
<td>March 1, 2017</td>
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<td>Osteoarthritis*</td>
<td>Arthritis Foundation</td>
<td>March 8, 2017</td>
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<td>Spinal Muscular Atrophy**</td>
<td>Cure SMA</td>
<td>April 18, 2017</td>
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<tr>
<td>Friedreich's Ataxia**</td>
<td>FA Research Alliance</td>
<td>June 2, 2017</td>
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<tr>
<td>Tuberous Sclerosis (B LAM)**</td>
<td>Tuberous Sclerosis Alliance</td>
<td>June 21, 2017</td>
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<tr>
<td>CG1, a rare kidney disease**</td>
<td>National Kidney Foundation</td>
<td>August 4, 2017</td>
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<tr>
<td>Lupus**</td>
<td>LADA, LFA, L RJF</td>
<td>September 25, 2017</td>
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<td>Hyperhidrosis</td>
<td>International Hyperhidrosis Society</td>
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<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Parent Project Muscular Dystrophy</td>
<td>March 5, 2018</td>
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<td>Am. Partnership for Eosinophilic Disorders</td>
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<td>PC Project</td>
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<td>Epidermolysis Bullosa**</td>
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<td>Sleep Apnea</td>
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<td>Barth Syndrome**</td>
<td>Barth Syndrome Foundation</td>
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<td>Juvenile Idiopathic Arthritis</td>
<td>Arthritis Foundation: CARRA</td>
<td>August 2, 2018</td>
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<td>Alport Syndrome**</td>
<td>National Kidney Foundation</td>
<td>August 3, 2018</td>
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<td>Chemotherapy-induced hearing loss in pediatric cancers**</td>
<td>Children's Cause for Cancer Advocacy</td>
<td>September 13, 2018</td>
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<td>CMF &amp; Inherited neuropathies**</td>
<td>Hereditary Neuropathy Foundation</td>
<td>September 28, 2018</td>
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<td>Chronic hypophosphatemia**</td>
<td>XLH Network</td>
<td>October 5, 2018</td>
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<td>Cystic Fibrosis**</td>
<td>Cystic Fibrosis Research, Inc.</td>
<td>October 29, 2018</td>
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<td>Major Depressive Disorder</td>
<td>Despreession and Bipolar Support Alliance</td>
<td>November 16, 2018</td>
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<td>Niemann-Pick Type C</td>
<td>Ara Parseghian Medical Research Fund</td>
<td>March 18, 2019</td>
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<td>Mitochondrial Diseases**</td>
<td>United Mitochondrial Disease Foundation</td>
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<td>IgA Nephropathy**</td>
<td>National Kidney Foundation</td>
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<td>Myeloproliferative neoplasms**</td>
<td>AMR Research Foundation</td>
<td>September 16, 2019</td>
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<td>Pyruvate Kinase Deficiency**</td>
<td>National Organization for Rare Diseases</td>
<td>September 20, 2019</td>
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<tr>
<td>Eczema**</td>
<td>More Than Skin Deep Collaborative</td>
<td>September 23, 2019</td>
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<tr>
<td>CDKL5 Deficiency Disorder (CDD)**</td>
<td>LouLou Foundation</td>
<td>November 1, 2019</td>
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<tr>
<td>Lennox-Gastaut Syndrome</td>
<td>LGS Foundation</td>
<td>November 1, 2019</td>
</tr>
</tbody>
</table>

*HPM helped organize.  ^HPM moderated.  ^HPM aided with Voice of Patient report only.
Shift to Statute: 21\textsuperscript{st} Century Cures Act

Signed into law December 13, 2016

Requires FDA to make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of an approved NDA or BLA.

This includes the following information:

Data that are collected to provide information about the patients’ experiences with a disease or condition, including related to the impact of the disease on patients’ lives and patient preferences with respect to treatment;

Information on patient-focused drug development tools (e.g., Patient-Reported Outcome measures); and

Other information FDA determines to be relevant.
FDA PFDD Guidance Series: Enhancing the Incorporation of the Patient’s Voice in Medical Product Development and Regulatory Decision Making

Collecting Comprehensive and Representative Input (Draft June 2018)
- Defining research objectives and questions, and study design
- Key consideration: representativeness
- Extensive listing of methods for collecting and analyzing patient experience data

Methods to Identify What is Important to Patients (Draft Sept. 2019)
- Focus on burden of disease and burden of treatment to guide medical product development, including endpoint development
- Methods to elicit what is important to patients, e.g., to inform selection/development of COAs
- Approaches to asking the right questions
- Considerations for specific populations (children, cognitively impaired, rare diseases) and culturally diverse populations

Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments (Discussion Document: Oct. 2018)
- Mirrored elements of PRO guidance, applying patient-focused principles to all COAs
- More to come in CORE presentation

Incorporating COAs into Endpoint for Regulatory Decision Making (Discussion Document: Dec. 2019)
- Focus on FDA’s considerations for when a COA in a clinical study will be used to support regulatory decision-making
- Considerations for defining or constructing an endpoint
- Issues that can impact measurement’s interpretations
- How are data summarized and analyzed
- Establishing meaningful within-patient change

Emerging Methods: Patient & Caregiver Perception of Change Video Interviews

A technology to fully maximize each patient’s contribution to the scientific data, providing a breadth and depth of insight into their experience in the clinical trial.
P/CPC Video Interview Methodology

- Preliminary unstructured qualitative interviews
  - With patients and caregivers before initiating a study
  - Help to better understand:
    - Symptoms of the condition
    - Natural history
    - Impact on patient function
    - Quality of life
    - Outcomes important and relevant to the patient
  - Informs development of semi-structured interview guides
- Baseline, during, and post-trial video interviews
  - Gathers data on patients experiences with the drug or control
  - Can allow patients to visually demonstrate a treatment impact
  - Mobile applications are one of the most useful ways to conduct these interviews at the convenience of the patient and caregiver without interrupting their daily lives and inserting clinic-visit biases
Videos and Semi-Structured Interviews

Example: Barth Syndrome*

12-Week Pivotal Trial Followed by Open Label Extension (OLE)

Primary Endpoints
- Distance walked (meters) on 6MWT
- Total fatigue score on BTHS-5A

Secondary Endpoints
- Functional assessments (SWAY, HHD, 5XSST, CGI-S)
- Patient-reported outcomes (PGI-S, PROMIS Fatigue)
- Safety and tolerability
- Laboratory assessments (MLCL:L4-CL ratio)

Key Inclusion Criteria
- Genetically confirmed BTHS
- Males age ≥12 y
- Ambulatory and impaired during 6MWT
- On stable medication for 30 d prior to baseline visit

*Information, graphics, and videos were shared by Stealth BioTherapeutics and Casimir Trials.
Example: Barth Syndrome*

- Qualitative Interview Study
  - Completed after Part 1 (while still masked to treatment assignment)
  - Used a semi-structured interview guide
  - Used a HIPAA-compliant mobile app to record interview
  - Patients/Caregivers could have an interview partner video record the interview or could do a selfie interview

- Patients and caregivers were blinded to patient treatment status during Part 1 at the time of the interview

- Study staff were blinded to patient treatment status during Part 1 until after study completion and report submission

*Information, graphics, and videos were shared by Stealth BioTherapeutics and Casimir Trials.
Videos and Semi-Structured Interviews (cont.)

- Example: Barth Syndrome*

*Information, graphics, and videos were shared by Stealth BioTherapeutics and Casimir Trials.
### Videos and Semi-Structured Interviews (cont.)

#### Example: Barth Syndrome*

<table>
<thead>
<tr>
<th>S=Subject</th>
<th>C=Caregiver</th>
<th>Response to questions in module asking for comparison between daily life/specific symptoms today compare to before Part 1, Treatment Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>101-001 (S)</td>
<td></td>
<td>“I went to [Eagle Scout Camp] in Indiana this past summer where I walked a minimum of five miles a day. Yeah, up and down hills, minimum of five miles a day...So my movement and mobility is much, much better than what it used to be. I could never do that before the shots.”</td>
</tr>
<tr>
<td>101-003 (S)</td>
<td></td>
<td>“I haven’t noticed any change.”</td>
</tr>
<tr>
<td>101-004 (C)</td>
<td></td>
<td>“For instance, the traveling. Making our way through Atlanta airport before he started the shots, he would have to stop and take breaks. After he was on the medication—not so much. He still did walk a bit slower, but we can make it through the airport a lot faster when he was on the shots.”</td>
</tr>
<tr>
<td>101-005 (S)</td>
<td></td>
<td>“[W]hat stands out to me is the walking to the stop sign and back. I would walk the dog and before, I couldn’t even make it to the stop sign. And now, and even then, I would take breaks along the way. And now, I make it to the stop sign and back without taking any breaks. And I recover a lot faster from it, too.”</td>
</tr>
</tbody>
</table>

*Information, graphics, and videos were shared by Stealth BioTherapeutics and Casimir Trials.*
Videos and Semi-Structured Interviews (cont.)

- Example: Barth Syndrome*

*Information, graphics, and videos were shared by Stealth BioTherapeutics and Casimir Trials.
Value of PPC/CPC in Rare Diseases

- A need for a way to systematically assess and capture patient experiences because:
  - Heterogeneity in clinical phenotype and course
  - Lack of fit-for-purpose, sensitive outcome measures
  - Not able to predict different ways treatment benefit might manifest
- Can help avoid Type 2 error - a beneficial effect is not identified when in fact there is one
  - Because the benefit might have been missed by traditional endpoints
- Can help provide context to treatment benefits captured by trial endpoints
  - Understand why the level of improvement seen is clinically meaningful to patients
  - Help understand how benefits in trials result in improvements in activities in daily life and QoL
Conclusions
What Can We Take Away From FDA’s Evolving PFDD Approach?

- While patient engagement has been ongoing at FDA since 1980’s HIV/AIDS crisis, last 5-10 years a culture shift has occurred that values expertise of patients.

- Led to expansion of avenues for engaging patient communities, initially through more traditional government means (i.e., meetings) but starting to shift to broader methods.

- FDA is beginning to articulate where patient input can help inform decisions about product development and review (e.g., COA and endpoint development, benefit-risk decisions).

- Agency is shifting burden of collecting information from FDA to external stakeholders, both patient groups and industry.
PFDD Resources

- CTTI Patient Groups & Clinical Trials
  - Recommendations Document

- FDA PFDD Guidance Documents

- FDA Patient Engagement Programs & Initiatives
  - FDA Patient Representative Program
  - FDA Patient Listening Sessions
  - PFDD Initiative
THANKS!

You can find me at jvalentine@hpm.com
Patient Engagement in R&D

Backup Discussion
Janet Woodcock’s “Roadmap to Advocacy” Speech (Jan. 21, 2015)

- Key issue: often, by the time FDA has an opportunity to engage with a sponsor, many opportunities for engagement and critical decisions about the development program have been made.
- Key takeaway: patient groups should engage early and often with clinical trial sponsors to inform research planning.
- Described 10 different recommended roles and activities for patient groups to consider for engagement in the clinical trial enterprise (e.g., conduct registries/natural history studies, describe unmet needs of patients, advocate for inclusion of patient-centric outcome measures, be a ready source of reliable information).

Patient Group Engagement Across the Clinical Trial Continuum
From Bench to Bedside and Back

- Direct funding and fund raising for research or product development
- Natural history database/registry support
- Help define eligibility criteria within the study protocol
- Feedback on meaningful clinical endpoints
- Assist in creating the informed consent form
- Advise on study recruitment
- Accompany sponsor to FDA to advocate study design

- Direct funding and fund raising for trial operations support
- Network recruitment / outreach
- Serve on a Data Safety Monitoring Board
- Report on patient feedback regarding sites, investigators, and study participant experience
- Serve in preference studies for benefit-risk assessment

- Natural history database / registry support
- Provide feedback on how the patient community views results
- Help return study results to participants
- Write newsletter articles or blog about results
- Co-present results
- Serve on post-market surveillance initiatives

Pre-Discovery | Pre-Clinical | Phase 1 | Phase 2/3 | FDA review & approval | PAS/Outcomes

- Interest of research question to patient community
- Provide data on unmet need and therapeutic burden
- Direct funding and fund raising for research or product development
- Understanding mechanisms of action relevant to disease and symptom burden

- Network recruitment / outreach
- Direct funding and fund raising for research or product development
- Infrastructure support
- Provide input on study design (barriers to participation)
- Support trial awareness and recruitment
- Peer advocate during informed consent procedure

- Serve on FDA advisory committees
- Provide testimony at FDA hearings
- Feedback on meaningful clinical endpoints

*Adapted from Parkinson’s Disease Foundation materials for CTTI’s Patient Groups & Clinical Trials Project*
Measured Value of Patient Engagement in R&D

- Up-front patient engagement has been found to:
  - Avoid protocol amendments
  - Improve enrollment, adherence, and retention
  - Increase probability of product launch

- Resulting expected net present value (financial model that integrates cost, time, revenue, and risk) in typical oncology development programs entering phase 2 or phase 3 (assumes $100,000 investment in patient engagement):
  - Estimated $62 million for pre-phase 2 and $65 million for pre-phase 3
  - Equivalent of accelerating a pre-phase 2 product launch by 2.5 years or a pre-phase 3 product launch by 1.5 years

- Sources:
Emerging Methods: Patient Preference Studies

Backup Discussion
Patient Preference Study

Case Study: Hycela (Rituxan SC)

<table>
<thead>
<tr>
<th>IV administration</th>
<th>SC administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-specific dosing based on height and weight</td>
<td>Fixed dosing for all patients (no dose calculation required)</td>
</tr>
<tr>
<td>Prepare and dilute into IV bag</td>
<td>Ready to use vial</td>
</tr>
<tr>
<td>Infusion time: 1.5 to 4 hours</td>
<td>Injection time: 5-7 minutes</td>
</tr>
</tbody>
</table>
Patient Preference for Rituximab SC PrefMab (NHL): PPQ Results at Cycle 8

Reasons for preference

- Requires less time in the clinic (69%)
- Feels more comfortable during administration (37%)
- Feels less emotionally distressing (29%)
- Lower level of injection site pain (16%)

IV preferred (7% strong preference)

No preference

81% SC preferred (74% strong preference)
Rituxan Hycela - Patient Experience Data Submission (summary data from a patient preference study)

### Patient Experience Data Relevant to this Application (check all that apply)

<table>
<thead>
<tr>
<th>Description</th>
<th>Section where discussed, if applicable</th>
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<tbody>
<tr>
<td>The patient experience data that was submitted as part of the application, include:</td>
<td></td>
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<tr>
<td>Clinical outcome assessment (COA) data, such as</td>
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<tr>
<td>Patient reported outcome (PRO)</td>
<td>Section 8.1.1 Study endpoints</td>
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<tr>
<td>Patient reported outcome (ObsRO)</td>
<td>Section 8.1.2 Study results</td>
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<tr>
<td>Clinician reported outcome (ClinRO)</td>
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<tr>
<td>Performance outcome (Perfo)</td>
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<tr>
<td>Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)</td>
<td>Section 8.1.3 Study endpoints</td>
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<tr>
<td>Patient-focused drug development or other stakeholder meeting summary reports</td>
<td>Section 8.1.4 Study results</td>
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<td>Observational survey studies designed to capture patient experience data</td>
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<td>Natural history studies</td>
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<td>Patient preference studies (e.g., submitted studies or scientific publications)</td>
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<td>Other: (Please specify)</td>
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<tr>
<td>Patient experience data that was not submitted in the application, but was considered in this review.</td>
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14.4 Patient Experience

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin's lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400 mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.