PLASMA PROTEIN THERAPEUTICS ASSOCIATION

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FINAL SUMMARY
PPTA-FDA LIAISON MEETING

November 08, 2023
Virtual

Welcome and Introduction

PPTA opened the meeting with introductory remarks, welcomed all participants and expressed appreciation on FDA's participation in the meeting. PPTA's External Legal Counsel advised the participants on the meeting guidelines and the antitrust statement.

Brief Industry Update

PPTA presented FDA with industry updates, including International Quality Plasma Program (IQPP) updates, federal updates, and communications updates. For the IQPP the introduction of a new Donor Health Standard, revisions to the Plasma Collection Facility Standard, and the approval of final revisions to the IQPP Standards Program Description were discussed. Ongoing reviews include Personnel Education and Training Standard and Program Policy and Procedures. Efforts are underway to rebrand the IQPP for a renewed focus on donor health, safety, and quality improvement. On the federal front, the Plasma Caucus is operational, aiming to raise awareness among congressional members about plasma's critical role in treating rare diseases and encouraging their participation. Additionally, PPTA shared examples of proactive communications undertaken this year to include the Congressional Fly-in to further emphasize the significance of plasma donation and its economic impact on policymakers.

Brief FDA Update

The Office of Blood Research and Review (OBRR) shared details on Prelicensure/Preapproval Inspections, distinguishing between Prescription Drug User Fee Act (PDUFA) and Nonuser fee submissions. The discussion covered performance measures, individual risk-based assessments related to pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), as well as considerations for holding an educational webinar for Source Plasma (SP) Biologics License Applications (BLAs).

Improvements made through inspection process enhancements from 2020 to 2022 were shared with PPTA, the FDA emphasized the ongoing shift to a team-based approach involving Regulatory Project Management Staff (RPHMs) and Chief Scientific Officer (CSO) teams, aligning the Biologics Processing and Testing Branch (BPB) with the managed review process within the agency.

FDA further remarked proactive monitoring of turn-around-time and milestones, voluntarily following PDUFA timelines for non-PDUFA submissions, with OBRR continuing to lead these inspections. Additional information was shared about PDUFA VII, federal regulations, fee structures, performance goals, and distinctions between PDUFA and Non-User fee inclusions and exemptions. The Agency's key focus was on assessment of data related to HIV Individual

Risk-Based assessment (IRA) and impacts of PrEP and PEP, including regulatory guidance and recommendations, as well as insights into potential delays in HIV detection caused by certain medications and the FDA's recommendation for deferral of donors on PrEP and PEP to ensure blood safety.

PPTA inquired about accessing reports via the FOIA pathway and raised concerns about variations in denominator levels from 2017 to 2021, particularly the impact of COVID-19 in 2020. There was a call to revisit past involvements, including reviewing historical news reports, and strong support for an educational webinar.

Donor Health

PPTA shared updates on Donor Health Initiatives– Past, Current, and Future highlighting the significant role of the United States as the primary supplier of SP for plasma-derived medicinal products (PDMP) worldwide. Despite longstanding FDA regulations ensuring SP donor safety, inquiries persist, especially from European regulatory authorities. Notably, PPTA expressed interest in collaborating with the FDA on future donor studies, specifically focusing on long-term health effects of SP donation, seeking input on primary health and safety concerns, and exploring potential engagement with European partners for SP donor study design discussions, to help alleviate any perceived conflicts of interest with industry performing an industry funded study.

FDA conveyed that there are no available funds for studies at present. The ADVANCE study was conducted in other FDA offices, the Office of Biostatistics and the Office of Pharmacovigilance, and discussions can occur with them. It was acknowledged that there are challenges in data collection, statistical design, and interpretation, and the emphasis was placed on offering expertise in various research areas. FDA stated that although they advise on study design, they do not fund nor collaborate on publishing results, recognizing mutual concerns about donation frequency and limits, along with a lack of published evidence in certain areas of study, emphasizing that while they have influenced certain policies in the past, the do not have purview on other-on-other jurisdictions' decisions.

The FDA mentioned NIH-sponsored transfusion studies in the past, considering this avenue for obtaining funding and utilizing expertise of the NIH in clinical trial designs and related areas

Ensuring Consistency in Regulatory Communication and Approach

PPTA presented the objective of seeking collaborative solutions and industry previews on policy changes affecting the SP industry. PPTA suggested joint information exchanges akin to stakeholder comments on draft guidances as these would assist resolving existing communication and compliance challenges, including consistent regulatory interpretations and enforcement from the FDA related to, amongst others 21CFR610.40 and 21CRF630.30 PPTA emphasized proactive communication for adjustments to ensure compliance. PPTA's members are committed to high compliance standards, deviation management procedures, with discussions on deviations observed during license approval inspections and changes in industry-wide practices. This includes minimum volume testing, donor suitability, and unit suitability interpretations. PPTA inquired whether the FDA would be open to engaging in a

collaborative information exchange akin to public stakeholder comments on policy changes influencing the source plasma industry.

In response, the Agency aimed to ensure consistent communication and address process changes for managing teams, reconciling record reviews and in-person inspections. FDA clarified that their interpretation of regulations hadn't changed but aimed to ensure blood establishment practices adhered to regulations. Observations of non-compliant practices triggered discussions and appropriate actions for clarification with individual blood establishments, acknowledging each establishment's uniqueness. The agency actively engaged in inspections, communicating with team leads and other branches to maintain consistent practices.

FDA also noted that the minimum volume guidelines don't demand every donation to be tested, acknowledging scenarios where testing might not occur. Observations revealed hundreds of milliliters of unused plasma being discarded without testing, a contrast to the transfusion system's limited untested blood donations. The CFR emphasizes donations intended for manufacturing, outlining expectations defined in regulations, despite occasional situations where donations can't be tested. Clarifications were provided to dispel the misconception that every donation is mandated for testing, noting discrepancies between practices within the source plasma operation and transfusion systems.

FDA Individual Risk Assessment (IRA) Guidance

PPTA presented updates on the implementation of the FDA Individual Risk Assessment (IRA) Guidance. PPTA's members are diligently working to implement the guidance, this includes updates to donor management systems. PPTA requested clarification on defining a "new sexual partner" and clarifying incarceration criteria as per the FDA's Compliance Policy. Further discussion explored SP donation eligibility of frontline responders and healthcare workers taking PrEP and whether industry could support changes to policy with data collection and risk assessment evaluations.

FDA acknowledged the SP industry's need for retaining restrictive questions for alignment with other jurisdictions' regulatory authorities. Regarding "new partner" definition, it is the decision of the responsible physician or designee to determine eligibility, however consideration is given to ongoing relationships versus those that ended with additional sexual exposures, affecting the risk of window period donations. Examples given included spousal relationships, emphasizing that if a relationship ended, potentially leading to further sexual exposures, it would be classified as a new partner, affecting the eligibility determination.

FDA clarified that the Compliance Policy doesn't extend to unsuitable donations due to incarceration, particularly for transfusion transmitted infections. While recognizing the discrepancy between the 12-month deferral in the Final Rule and the three-month deferral in the HIV guidance, current assessments adhere to the regulatory timeframe. However, there is a consideration underway for regulatory changes to align with other deferral periods for HIV risk based on supportive data.

In conclusion, FDA noted that questions about guidance implementation should be communicated for further discussion; the need for a standalone guidance will be addressed upon review.

Inspections of SP collection establishments: Feedback from Industry on OBRR's Regulatory Processes and Approaches; Follow-up from 2022 meeting

PPTA recognized FDA's ongoing efforts to monitor this process are appreciated, highlighting the value for continuous improvement in managing reapproval inspections, and submissions.

FDA answered the following questions:

1. Is there a pathway within current OBRR processes to reduce existing compliance check requirement, if multiple centers managed by the same applicant/ member company are pending BLA approval?

FDA noted that it's crucial to perform a compliance check for every BLA, particularly for a supplement at a new facility, as there are no alternatives to bypass this process.

2. What steps does OBRR take to ensure a general scheduling, consistent inspection and BLA issuance process?

FDA propose that members directly contact the regulatory health project managers responsible for overseeing the review process.

3. In view of the growing number of new SP centers seeking licensure, what other efficiencies is the OBRR currently investigating to enhance the BLA approval process?

While FDA diligently adheres to internal submission timelines, the quality of some submissions influences turnaround times. FDA hence recommends that new establishments submit complete and high-quality applications to expedite the review process.

2023 FDA Immune Globulin Hypersensitivity Reactions Public Workshop; Follow-up from discussions on donor deferral

The presentations focused on the possible avenues to defer donors which have been identified as responsible for causing hypersensitivity reactions in recipients of specific Immune Globulin lots.

The FDA explained the impact of such products on patients, including discomfort and anxiety, leading to concerns about their next immune globulin, additional medications for treating reactions, and possible under-treatment due to incomplete infusions and how investigations identified the responsible plasma donors. The affected manufacturers conducted substantial investigations to identify and test donors (19 in total identified up to date) responsible for these reactions but haven't yet been successful in fully understanding the root-causes. There is a need to manage identified donors effectively to prevent them donating in the future –

especially as some have been lost to follow-up and could donate at other manufacturers SP collection facilities.

PPTA presented the PPTA National Donor Deferral Registry (NDDR) as an existing pathway for permanently deferring donors who have tested reactive for HIV, HBV or HCV. While other deferral categories could be added, the NDDR system defers "Applicant Donors", hence "Qualified Donors" would not be identified. PPTA hence proposed that the FDA share the donor data across the entire industry to immediately retrieve affected units from the identified donors.

FDA also answered the following questions:

1. Can FDA clarify expectations for industry regarding management of identified donors?

FDA recognized the limitations of the NDDR and is willing to discuss any reporting mechanism proposed by PPTA, noting that the system might require adjustments.

2. Does FDA agree to industry-wide sharing of details of identified donors immediately so companies can identify take actions promptly, such as retrieving affected units?

The FDA acknowledged the importance of sharing information about these identified donors across the industry for potential deferral actions. Nevertheless, in response to the question about the 19 donors, the FDA highlighted the necessity of initial discussion with colleagues in OTP before advancing further.

Industry Emergency Preparedness and Hyperimmune Globulin/Convalescent Plasma Planning

PPTA presented on initiatives and plans for disaster preparedness in potential future pandemics or emerging TTIs. PPTA highlighted the "lessons learned" during the COVID-19 pandemic regarding the establishment and management of SP collections. Specific regulatory flexibilities, including FDA's guidances, as well as guidance issued by the HHS were key to maintaining operations, particularly for patients with primary immune deficiencies. PPTA highlighted the industry's joint engagement in developing a COVID-19 hyperimmune IG as well as collaborating with multiple entities, including the NIH and regulatory agencies. Lastly, PPTA noted the history of dealing with emerging infectious diseases, relying on the expertise of the global pathogen safety working group.

Question for the FDA:
Does the FDA have any specific recommendations for the SP industry regarding future disaster planning?

FDA acknowledged the evolving understanding of convalescent plasma's role during the pandemic, with increased appreciation driven by numerous publications. FDA suggested the need for a future debrief to assess both successful and problematic aspects of convalescent plasma utilization during the COVID-19 pandemic. A key lesson highlighted was the

importance of having the correct analytics for effective use. The FDA expressed gratitude for the industry's input and noted that many of the challenges encountered in the plasma sector also apply to safety surveillance and other product-related challenges. They encouraged future discussions to explore potential improvements and a move towards a federated system.

Closing Remarks

PPTA thanked the FDA for their time and willingness to continue to have this liaison meeting and thankful for their international leadership. FDA stated they were appreciative of the engagement.

Action points:

- **PPTA to explore the possibility of securing funding and leveraging the expertise of the NIH in clinical trial designs and related areas by investigating the FDA-mentioned NIH-sponsored transfusion studies as a potential avenue.**
- **PPTA will initiate communication with the FDA to discuss questions regarding the implementation of guidance and address the consideration of a standalone guidance after the review process.**