CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761036Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	761036
Applicant Name	Janssen Biotech, Inc.
Date of Submission	July 9, 2015
PDUFA Goal Date	March 9, 2016
Proprietary Name / **Established (USAN) Name**	DARZALEX/daratumumab
Dosage Forms / Strength	100 mg/5 mL in a single use vial 400 mg/20 mL in a single use vial
Proposed Indication(s)	a human anti-CD38 monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent
Action/Recommended Action for NME:	**Accelerated Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Barry Miller, MSN, CRNP, Albert Deisseroth, M.D., Ph.D.,
Statistical Review	Yaping Wang, Ph.D., /Yuan Li-Shen, Dr. Ph./ Raji Sridhara, Ph.D.
Pharmacology Toxicology Review	Emily Place, Ph.D., M.P.H./ Christopher Sheth, Ph.D./ John Leighton, Ph.D.
CMC Review/OBP Review	Jibril Abdus-Samad, Pharm.D./Tura Camilli, Ph.D./ Wayne Seifert/Laura Fontan/Zhihao (Peter) Qiu, Ph.D./Jee Chung, Ph.D./Sarah Kennett, Ph.D./Kathleen A. Clouse Strebel, Ph.D.
Microbiology	Natalia Pripuzova, Ph.D./Maria Jose Lopez Barragan, PhD./Patricia Hughes, Ph.D.
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach, Ph.D./Bahru Habtemariam, Pharm.D./Lian Ma, Ph.D./Robert Schuck, Pharm.D., Ph.D./Nitin Mehrotra, Ph.D.
OSI	Anthony Orencia, M.D./Susan Thompson, M.D., M.P.H., Kassa Ayalew, M.D., M.P.H.
CDTL Review	Albert Deisseroth, M.D., Ph.D.

OSE	Nisha Patel/Kathleen Davis, RN/Michele Rutledge, Pharm.D./Yelena Maslov, Pharm. D./Rowell Medina, Pharm.D./Barbara Fuller, RN, MSN, CWOCN/ LaShawn Griffiths, MSHS-PH, BSN, RN
QT-IRT	Jiang Liu, Moh Jee NG, Qianyu Dang, Michael Y Li, Norman L Stockbridge, M.D.
CDRH	Jennifer Dickey/Donna Roscoe/Reena Philip
DPMH	Suchitra M. Balakrishnan, MD, PhD.,/Tamara Johnson, MD, MS,/Lynne P. Yao, MD,

Signatory Authority Review Template

1. Introduction

On July 9, 2015 Janssen has submitted a Biologics Licensing Application for DARZALEX, a human anti-CD38 monoclonal antibody (IgG1κ) indicated for the treatment of patients with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent.

Breakthrough Therapy Designation was granted on May 1, 2013.

This application was given priority review. No monoclonal antibodies directed against CD38 are approved at this time for treatment of multiple myeloma.

DARZALEX is not approved in any country at this time.

2. Background

Multiple myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant cured of their disease. The classes of agents used to treat multiple myeloma include: steroids, alkylators, histone deacetylase inhibitor, proteasome inhibitors, and immunomodulatory agents. The development and approval of proteasome inhibitors and thalidomide analogues has improved the outlook for patients with multiple myeloma with a current median overall survival of approximately 5 years. However to continue to make progress for patients with multiple myeloma additional therapies with differing mechanisms of action and adverse event profiles are needed.

The Applicant has submitted the results from a single arm trial enrolling patients with relapsed disease to treatment with daratumumab. This trial is supported by other single arm trial data.

3. CMC/Device

No issues were identified that would preclude approval.

From the review:

Daratumumab is supplied as a colorless to pale yellow, preservative-free sterile solution for intravenous infusion:
100 mg/5 mL single use vial
400 mg/20 mL single use vial

From the Micro review:
Following dilution the infusion bag/container may be stored for up to 24 hours at refrigerated conditions, protected from light. After allowing the bag/container to come to room temperature, DARZALEX solution has to be used immediately. Infusion should be completed within 12 hours. Any unused portion of the infusion solution should not be used.

Daratumumab should be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) and protected from light. This product contains no preservative.

The product shelf life recommendation is for 18 months stored at 2-8 C.

From the Facilities review 11/12/15:
Compliance decisions for the (b) (4) /2015 inspection of the (b) (4) and the 10/5-9/2015 inspection of the Janssen Biologics site (FEI 3007029098) proposed for (b) (4) DS manufacture are complete and acceptable. This application is recommended for approval from a facilities standpoint.

The following PMR/PMCs are recommended (text taken from the review):

PMR 1: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.
PMR 2: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

PMR 3: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.
PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b) (4) *and drug substance long term storage containers.*
PMC 3: Re-evaluate (b) (4) *lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.*
PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the secondary review:

According to the Applicant, daratumumab is designed to target CD38 positive B-cells and plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme involved in the production of nucleotide metabolites. CD38 is highly expressed in human hematopoietic cells/tissues, and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone. Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or

HuMab-3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). The in vitro studies demonstrated that daratumumab and HuMab-CD38 bound to purified human CD38 with high affinity as shown by KD values in the low nanomolar (nM) range. Both antibodies also bound to several lymphoma cell lines. Daratumumab induced myeloma tumor cell lysis through complement-dependent cytotoxicity (CDC), whereas HuMab-CD38 has far less CDC activity. Daratumumab,HuMab-CD38 and rituximab were shown to elicit similar maximal lysis (approximately 40%) of lymphoma cells in vitro through antibody-dependent cell-mediated cytotoxicity (ADCC), and daratumumab is approximately twice as potent as either HuMab-CD38 or rituximab. Daratumumab and a variant (DARA-K322A) with an altered residue in the Fc region were shown to induce macrophage-mediated phagocytosis (antibody-dependent cellular phagocytosis (ADCP)) in malignancies expressing CD38. Daratumumab also promotes apoptosis through Fc mediated cross-linking, in vitro.

Pharmacology studies also indicate daratumumab modulates CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38, whereas the surrogate HuMab-CD38's ability to inhibit ribosyl cyclase enzyme activity is substrate dependent and it conversely inhibits cADPR hydrolase activity. Importantly, the degrees to which the known mechanisms contribute to the clinical efficacy of daratumumab is still unknown. In vivo pharmacology studies showed that daratumumab reduced tumor growth and burden in human lymphoma xenograft mouse models. Based on the nonclinical data submitted in the BLA and its chemical structure, the Established Pharmacological Class (EPC) of "human CD38-directed monoclonal antibody" was determined to be both clinically meaningful and scientifically valid for Darzalex (daratumumab).

Stand-alone safety pharmacology studies were not conducted with daratumumab. ECG parameters, respiratory rates, body temperatures and pulse rates were assessed during the 6-week repeat-dose toxicology study in chimpanzees and were unremarkable at doses up to 25 mg/kg. ECGs, body temperature and heart rate were assessed during the 2 week repeat dose toxicology study in monkeys and were unremarkable at doses up to 100 mg/kg.

The toxicology data for daratumumab was generated in the chimpanzee (in study that was not designed to be terminal and was not requested by the FDA), and in the monkey using the HuMab-CD38 surrogate antibody. These studies indicated there are no gender differences in exposure in chimpanzees or monkeys. Increases in Cmax and AUC values are greater than dose proportional in the chimpanzee, and approximately dose proportional in monkeys. Daratumumab was slowly eliminated in

the blood following intravenous dosing with half-lives of approximately 15.5 to 18.8 days in chimpanzees, and 9 to 63 hours for HuMab-CD38 in the monkey.

The general toxicology studies reviewed were a 6-week repeat-dose toxicity study in chimpanzee and a 2-week repeat dose toxicity study in the monkey. Both repeat-dose toxicity studies utilized IV dosing, which is the intended route of administration for Darzalex. In animals, daratumumab was found to target the hematopoietic and lymphatic systems, in addition to the liver and spinal cord and nervous system. Findings include:

- *Hematopoietic and lymphatic systems: Increases in red blood cells, hemoglobin, and hematocrit; decreases in white blood cells and platelets (chimpanzee and monkey); lymphoid depletion/atrophy in thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch (monkey only).*

- *Liver: Elevated AST, ALT (chimpanzee only).*

- *Cytokine response reaction (chimpanzees only): Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest leading to one mortality.*

- *Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.*

The Applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. The considerations led to no reproductive and developmental toxicology studies being conducted for daratumumab include: the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); that these studies are not warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9). ICH S9 also outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies were needed.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified. The text below is from the executive summary of their review.

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that specifically binds to the CD38 protein expressed on the surface of

multiple myeloma tumor cells and other cell types at various levels. In vitro, daratumumab can induce tumor cell lysis through complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. The proposed indication is daratumumab for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. The proposed dosing regimen is 16 mg/kg body weight weekly on Weeks 1 to 8, every two weeks on Weeks 9 to 24 and every four weeks on Weeks 25 onwards until disease progression.

The population pharmacokinetic (PK) analysis included 223 patients with multiple myeloma who received daratumumab (150 subjects received 16 mg/kg). Over the dose range from 1 to 24 mg/kg, AUC increases more than dose-proportionally. Clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the recommended dose and schedule, the Cmax at the end of weekly dosing is 2.9-fold higher than following the first infusion. Daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period and the Cmax at steady-state to Cmax after the first dose is 1.6. The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance is approximately 18 (9) days.

Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also show that age (31-84 years), gender, mild to severe renal impairment (15 to 89 mL/min) and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis shows that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations (Cpre-infusion, max) ≥ 270 µg/mL. Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab Cpre-infusion,max < 270 µg/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations > 270 µg/mL. However, this analysis was confounded by baseline risk factors such as disease severity. Patients with lower exposure who did not respond to treatment were also the patients with higher disease burden, worse performance status (Eastern Cooperative Oncology Group [ECOG]), and more advanced disease at baseline. Given that there is no control arm available in these open-label trials, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. As such, we recommend that the applicant should evaluate the possibility of dose

optimization in these patients with lower exposure when more data are available from the ongoing controlled clinical trials. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trials MMY2002 and GEN501.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased rates of ≥ grade 3 treatment emergent adverse events (TEAE), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. Patients with moderate and severe hepatic impairment were excluded from the clinical trials, and there are no safety data in these patient populations. Recent literature data suggest that CD38 may play roles in normal hepatic function and liver disease. Therefore, patients with hepatic impairment may be sensitized to daratumumab through yet unknown mechanisms involving CD38. Additional data are needed to confirm this potential safety signal, and to characterize the safety of daratumumab in the patient sub-population with baseline hepatic impairment and multiple myeloma for which daratumumab may provide clinical benefit. A PMR is issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic function.

From the OT-IRT review:
No clear dose-dependent QTc effect was observed (see Table 8 and Table 9). Based on concentration-QTc analysis, no evident exposure-response relationship was observed after adjusting for infusion effect (Figure 5). The predicted ΔQTcF is less than 10 ms with upper bound less than 20 ms at the therapeutic Cmax of 1000 ug/mL, suggesting no clinically relevant QT prolongation of daratumumab.

Comment: I have read the reviews and am not sure the significance of the findings in patients who had mild hepatic impairment. The Agency will ask the company to further address this potential issue.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

The Applicant submitted data from two single arm trials: MMY2002 and GEN501.

GEN501 was a first-in-human phase 1/2 monotherapy dose-escalation trial in patients with relapsed or refractory multiple myeloma. The trial included dose escalation cohorts and explored various dosing schedules.

MMY2002 was an open-label, single arm, phase 2 trial enrolling patients with relapsed multiple myeloma who had received prior treatments including proteasome inhibitors and immunomodulatory agents. The trial tested two weekly dosing regimens. The clinical review focused on the 16 mg/kg weekly treatment. In this cohort 106 individuals received 16 mg/kg of daratumumab until disease progression.

The dosing regimen was 16mg/kg intravenously once every week for 8 weeks, then once every 2 weeks for 16 weeks, and then once every four weeks.

For both trials, the primary endpoint was overall response rate, calculated as the proportion of subjects who achieved a partial response (PR) or better during treatment or the follow-up phase. The MMY2002 trial results showed an ORR of 29% (95% CI: 21-39%) and with a median duration of response of 7.4 months. The GEN501 trial results for those 42 patients receiving 16 mg/kg dose regimen showed an ORR of 36% (95% CI: 22-52%) with a median DOR of 6.9 months.

I concur with the findings of the clinical and statistical review teams regarding approval of this product.

8. Safety

The major safety issues identified with use of this product in clinical trials include: infection, infusion–related reactions (needing pretreatment with steroids), fatigue, nausea, back pain, fever, and cough. The most common laboratory abnormalities were lymphopenia, neutropenia, anemia, and thrombocytopenia.

Two unique test interference issues are observed with this product:

1) Interference with Indirect Antiglobulin Tests resulting in interference in Blood Bank non-ABO/non-RhD antigen typing
Daratumumab binds to CD38 on RBCs and may interfere with compatibility testing, including antibody screening and crossmatching. Daratumumab does not interfere with ABO or Rh compatibility testing; however, may interfere with minor antigen testing. Interference mitigation methods include either treating reagent RBCs with dithiothreitol to disrupt daratumumab binding (antibody screen test) or antigen genotyping. Due to the fact that the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with cross-matching and red cell antibody screening was observed in less than 5% of patients enrolled in the clinical trials.

2) Interference with Serum Protein Electrophoresis and Immunofixation Tests resulting in interference with complete response determination
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of

complete responses by IMWG criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

The labeling will contain a warning about these issues.

9. Advisory Committee Meeting

No clinical efficacy or safety issues arose that required an Advisory Committee meeting.

10. Pediatrics

This product has orphan designation for this indication.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) report stated the following:
In summary, OSI considers that data from the above three clinical and sponsor sites are acceptable in support of the BLA.

Financial Disclosure information was provided and reviewed. None of the investigators had disclosable financial interests or arrangements.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval with post-marketing commitments to confirm clinical benefit

- Risk Benefit Assessment

Relapsed multiple myeloma is a serious and life-threatening illness without a curative therapy except for an allogeneic stem cell transplant. The typical clinical course for those who do not undergo a transplant is characterized by multiple relapses. While significant improvement in median survival for patients with multiple myeloma has been achieved with the recent approval of thalidomide analogues and proteasome inhibitors, additional therapies with different modes of action and adverse event profiles are needed. Daratumumab is a novel monoclonal antibody targeted against CD38 which is present on the surface of plasma cells and B-cells and through effector mechanisms such as complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and macrophage-mediated phagocytosis. In the single arm trial data submitted, daratumumab produced durable response rates of 29-36%. Patients need pre-

treatment with steroids to avoid infusion-related reactions. The major safety issues identified with use of this product in clinical trials include: infection, infusion–related reactions (needing pretreatment with steroids and other products), fatigue, nausea, back pain, fever, and cough. The most common laboratory abnormalities were lymphopenia, neutropenia, anemia, and thrombocytopenia. Two unique test interference issues are observed with this product: 1) Interference with Indirect Antiglobulin Tests resulting in interference in non-ABO/non-RhD antigen typing and 2) Interference with Serum Protein Electrophoresis and Immunofixation Tests resulting in interference with complete response determination.

The labeling will contain a warning about these issues.

- Recommendation for Post marketing Risk Management Activities – routine surveillance

- Recommendation for PMRs under accelerated approval

PMR-1 (AA) Submit the complete final report and data showing clinical efficacy and safety from trial MMY3003, a Phase 3, 2-arm, randomized, parallel-group trial of lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

PMR-2 (AA) Submit the complete final report and data showing clinical efficacy and safety from trial MMY3004, a Phase 3, 2-arm, randomized, parallel-group trial of bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

- Recommendation for PMRs not under accelerated approval

PMR-3 Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4. The assay must be capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

PMR 4: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR 5: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR 6: Collect additional data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.

Recommendations for PMCs

PMC 1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the [redacted] and drug substance long term storage containers.

PMC 3: Re-evaluate [redacted] lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 6:To provide data to demonstrate that the [redacted] validation studies of [redacted] has the same or better microbial growth promotion properties than the daratumumab [redacted]. In the event that the data fail to demonstrate the adequacy of the [redacted] additional studies will be performed to support the proposed [redacted].

Refer to action letter for final wording and milestones of the post-marketing requirements and commitments.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/13/2015