ASNC

NC TODAY 2018

BEST PRACTICES FOR TODAY, INNOVATIONS FOR TOMORROW

APRIL 20 – 22, 2018 | LOEWS CHICAGO O'HARE HOTEL

Course Directors:
Dennis A. Calnon, MD, MASNC
David G. Wolinsky, MD, MASNC

This two-and-a-half day interactive course for physicians, technologists and other healthcare professionals provides the latest updates in nuclear cardiology imaging. As an attendee, you will increase your knowledge and competency in solving clinical, technical and practical issues facing nuclear cardiology imaging professionals.

Among 2017 survey respondents who attended the 2½-day program held in Chicago last spring —

94% rated the Nuclear Cardiology Today content as USEFUL.
"Very applicable material to every day practice."

91% rated Nuclear Cardiology Today: EXCELLENT or VERY GOOD.

Save the Date! April 20-22, 2018

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2017 Program Schedule

Thursday, September 14

1:00PM – 2:30PM

C CORE

Session 101 How to Incorporate Test Findings Beyond Perfusion

Location: Chicago **CME: 1.5; CE: 1.25; MOC**

Moderators: *A. Iain McGhie, MD; Ibrahim M. Saeed, MD*

1:00PM Significant ST Segment Changes
Christopher L. Hansen, MD, FASNC

1:20PM Arrhythmias, Heart Rate Recovery and Abnormal Hemodynamic Responses
John Wells Askew, MD, FASNC

1:40PM High Risk MPI Markers
R. Parker Ward, MD, FASNC

2:00PM Coronary Artery Calcium and Coronary Flow Reserve
L. Samuel Wann, MD

2:20PM Discussion

O OTHER

Session 102 Positioning your Nuclear Cardiology Laboratory for Long-term Success: A Comprehensive Boot Camp - Part 1

Location: Empire BC **CME: 1.5; CE: 1.5**

Moderator: *Larry Sobal, MBA*

1:00PM - 2:00PM

Part 1. Operations: Optimal Staffing of the Nuclear Cardiology Laboratory in 2017

1:00PM Physician Supervision Requirements for Stress Testing in 2017
Lisa A. Oakes, RN

1:20PM What is the Ideal Staffing of a Nuclear Cardiology Laboratory?
Lisa A. Oakes, RN

1:40PM Do Nuclear Technologists Need Additional Training and Qualification to Perform PET, SPECT/CT, or PET/CT Imaging?
Robert A. Pagnanelli, CNMT, RT(N)(R), NCT, FASNC

2:00PM - 2:30PM

Part 2. The Economics of Nuclear Cardiology: Billing, Reimbursement, and Compensation

2:00PM How Do We Know We Are Billing Correctly?
TBD

2:15PM How to Work Effectively with RBM's to Facilitate Prior Authorization
Timothy M. Bateman, MD, MASNC

2:45PM – 4:00PM

MI MULTIMODALITY IMAGING

Session 103 CT, PET/CT and PET/MR Imaging to Assess Heart Disease

Location: Chicago **CME: 1.25; CE: 1.0; MOC**

Moderators: *Jamieson M. Bourque, MD, FASNC; John J. Mahmarian, MD, MASNC*

2:45PM Ancient to Current: CT in the Evaluation of Atherosclerosis in Populations
Gregory S. Thomas, MD, MPH, MASNC

3:00PM PET/CT: Current Role and Opportunities for Advancement
Mouaz H. Al-Mallah, MD, FASNC

3:15PM PET/CT: Current Role and Opportunities for Advancement
Andrew E. Arai, MD

3:30PM Case Presentation and Discussion

2:45PM – 4:15PM

O OTHER

Session 104 Positioning your Nuclear Cardiology Laboratory for Long-term Success: A Comprehensive Boot Camp - Part 2

Location: Empire BC **CME: 1.5; CE: 1.5**

Moderator: *Dennis A. Calnon, MD, MASNC*

2:45PM - 3:45PM

Part 3. Quality: Optimal Nuclear Cardiology Equipment and Protocols

2:45PM What Is the Ideal Mix of SPECT and PET Equipment for the Modern Nuclear Cardiology Laboratory?
Timothy M. Bateman, MD, MASNC

3:05PM How Do We Select the Appropriate Test and Protocol for the Patient Even if the Referring Physician Requested a Different Test?
Randall C. Thompson, MD, FASNC

2:45PM How Can We Incorporate AUC Into the Modern Nuclear Laboratory?
David G. Wolinsky, MD, MASNC

3:45PM - 4:15PM

Part 4. The Future Landscape of Healthcare and Reimbursement and the Impact on Nuclear Cardiology

3:45PM Where is the Industry Heading and How Should We Position Ourselves to be Successful in the Value World?
Larry Sobal, MBA

Thursday, September 14 (cont.)

4:15PM – 6:00PM

PP POLICY AND PRACTICE

Session 105 The Changing Face of Medicare: Considerations in Practice and Payment

Location: Chicago **CME: 1.5; CE: 1.25; MOC**

Moderators: *William A. Van Decker, MD, MASNC; Kim A. Williams Sr., MD, MASNC*

4:15PM Introductory Remarks
William A. Van Decker, MD, MASNC

4:25PM Coding Update
Georgia Lawrence

4:35PM MIPS/ MACRA- What You Need to Know
Kim A. Williams Sr., MD, MASNC

4:50PM System Level Considerations in Value-based Care
Jack A. Ziffer, MD, PhD, FASNC

5:05PM Bundled Payments for Care Improvement Initiative (BCPI)
Gregory S. Thomas, MD, MPH, MASNC

5:20PM Cardiac Bundled Payment in Practice: a Case Study from HeartWell LLC
Jonathan Fialkow, MD

5:35PM Medicare's Appropriate Use Criteria Program: an ASNC Status Update
L. Samuel Wann, MD

5:50PM Discussion

6:15PM – 7:15PM

AR ABSTRACTS/RESEARCH

Session 106 Rapid Fire ePosters: Disease-based — Amyloidosis

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussants: *Sabahat Bokhari, MD, FASNC; Edward J. Miller, MD, PhD, FASNC*

6:15PM 106-01 Simultaneous Dual Isotope Tc99m PYP/ Thallium-201 SPECT Myocardial Imaging Reduces the Frequency of Equivocal Tc 99m PYP SPECT Findings in Patients With Suspected Cardiac Amyloidosis Imaging With Thallium-201 SPECT Improves Certainty of Detecting Myocardial Uptake of Tc99m PYP Among Patients With Equivocal Imaging Findings
Yuka Otaki, MD, PhD; Balaji Tamarappoo; Yoav Arnson; Mhairi Doris; Heidi Gransar; Sean Hayes; John Friedman; Louise Thomson; Piotr Slomka; Damini Dey; Daniel Berman

6:25PM 106-02 On Close In-SPECT-tion, a Planar Technetium-99m Pyrophosphate Scan for Cardiac Amyloid is Not Enough
Imaad Razzaque, MD; Debra Mahlum; Khawaja Afzal Ammar; Steven Port

6:35PM 106-03 Tc-99m PYP Scan for Cardiac Amyloidosis: 1 Hour vs 3 Hour Imaging
Ahmad Masri, MD; Ricardo Nieves; Andrew D. Althouse; William Follansbee; Joao L. Cavalcante; Prem Soman

6:45PM 106-04 Apical Sparing of Longitudinal Strain Cannot be Explained by Regional Differences in Florbetapir Retention in Cardiac Amyloidosis
Paco E. Bravo, MD; Kana Fujijura; Marie F. Kijewski; Sophia Jacob; William Sticka; Shipra Dubey; Anthony Belanger; Mi-Ae Park; Marcelo F. Di Carli; Rodney H. Falk; Sharmila Dorbala

6:55PM 106-05 Clinical Utility of 99mTc-PYP and 201Tl-Cl SPECT Imaging in Patients with Suspected Cardiac Amyloidosis
Shimpei Ito, MD; Nobuhiro Kodani; Kazuaki Tanabe

7:05PM 106-06 Non-cardiac Uptake of Technetium-99m Pyrophosphate (TcPYP) in Cardiac Amyloidosis
Brett W. Sperry, MD; Richard Brunken; Manuel D. Cerqueira; Mazen Hanna; Wael A. Jaber

7:00PM – 9:30PM

LL LIFELONG LEARNING

Session 107 ASNC Maintenance of Certification Module 2

Location: New York/Atlanta **CME: 2.5**

Lead Facilitator: *Karthikeyan Ananthasubramaniam, MD, FASNC*
Facilitator: *Maria G. Sciammarella, MD; Ronald G. Schwartz, MD, FASNC*

Friday, September 15

7:45AM – 9:30AM

PL PLENARY

Session 201 Opening Plenary and Verani Lecture

Location: Exhibit Hall B **CME: 1.0; CE: 1.0**

Moderator: *Donna M. Polk, MD, MPH, FASNC*

7:45AM Opening Remarks from ASNC CEO
Kathleen Flood

7:55AM Remarks from the ASNC2017 Program Chair
Donna M. Polk, MD, MPH, FASNC

8:05AM President's Address — The Triple Threat One Year Later
Raymond R. Russell, III, MD, PhD, FASNC

8:20AM ASNC and ASE: Innovative Collaboration
Raymond R. Russell, III, MD, FASNC and Vera H. Rigolan, MD

8:25AM President Elect's Address - Nuclear Cardiology: The Case for Optimism
Prem Soman, MD, PhD, FASNC

8:45AM Presentation of the Kenneth Brown Award for Best JNC Editorial
Ami E. Iskandrian, MD, PhD, MASNC

8:50AM Introduction of the Mario Verani Lecturer
Raymond R. Russell III, MD, PhD, FASNC

8:55AM Mario Verani Lecture: Evolving, Innovating and Revolutionary Changes in Cardiovascular Imaging — We Have Only Begun!
Leslee J. Shaw, PhD, FASNC

Friday, September 15 (cont.)

9:30AM – 10:30AM

AR ABSTRACTS/RESEARCH

Session 202a ePosters: New Developments in Quality and Appropriate Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Robert C. Hendel, MD, MASNC*

9:35AM 202a-01 Prevalence of Ischemia on Rarely Appropriate Myocardial Perfusion Imaging: Validation of Appropriate Use Criteria
David E. Winchester, MD MS; Carsten Schmalfuss; Rebecca Beyth

9:45AM 202a-02 Usefulness of HEART Score with Coronary Artery Calcium Scores on the Prediction of Abnormal SPECT MPI Studies in Emergency Department Chest Pain Patients
Nissi Suppogu, MD; Alan W. Ahlberg; W. Lane Duvall, MD

9:55AM 202a-03 Implementation of the American Society of Nuclear Cardiology (ASNC) Recommendations Resulted in a Significant Reduction in Radiation Exposure Along With Improved Patient Satisfaction Score Without a Deterioration in Image Quality
Basant Arya, MD; Cynthia Meek

10:05AM 202a-04 The Impact of Appropriate Use Criteria on the Cost-Effectiveness of SPECT-MPI
Nathan L. Frogge, MD, MBA; Jagadish Khanagavi; Kathleen Hayes Brown; Rami Doukky

10:15AM 202a-05 Quality Improvement with Outpatient Myocardial Perfusion Imaging — Experience in a Managed Care Model
Avni Thakore, MD; Win Aung; Vikrum Malhotra

AR ABSTRACTS/RESEARCH

Session 202b Posters: Advances in PET Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Parthiban Arumugam, MB BS*

202b-01 Early Therapeutic Effects of Adaptive Servo-Ventilation on Cardiac Sympathetic Nervous Activity in Patients with Heart Failure Evaluated by the Combined Use of 11C-HED PET and 123I-MIBG SPECT
Yusuke Tokuda, MD; Keiichiro Yoshinaga; Mamoru Sakakibara; Kiwamu Kamiya; Kazunori Omote; Yoshiya Kato; Naoya Asakawa; Osamu Manabe; Nagara Tamaki; Hiroyuki Tsutsui

202b-02 18F-NaF Uptake and Evolution of Calcium Volume in the Process of Vascular Calcification
Takehiro Nakahara, MD, PhD; Jagat Narula; H. William Strauss

202b-03 Comparison of Diagnostic Accuracy of PET-derived Myocardial Blood Flow Parameters: A Meta-analysis
Sang-Geon Cho, MD; Soo Jin Lee; Yun Young Choi; Henry Hee-Seung Bom

202b-04 Anderson-Fabry Disease: Case Report Demonstrating Value of PET/CT in a Rare Disease
Abdul-rahman R. Abdel-karim, M.D; Abdelrahman Aly; Timothy M. Bateman

202b-05 Lack of Correlation of Segmental Myocardial Blood Flow versus Normalized Perfusion on Rubidium-82 PET in Patients with Angiographically Significant Coronary Disease
Cesia Gallegos, MD; Yi-Hwa Liu; Vera Tsatkin; Richard Palyo; Edward J. Miller

202b-06 Increasing Coronary Artery Calcium Burdens are Associated with Decreasing Global Stress Myocardial Blood Flow and Myocardial Flow Reserve
Hannah E. Raasch, MD; Raymond O. McCubrey; Viet T. Le; Steve O. Mason; Jon-David Ethington; Anjani Golive; Kent G. Meredith; Joseph B. Muhlestein; Kirk U. Knowlton

202b-07 Comparison of Gated 82Rb PET-CT with Cardiovascular Magnetic Resonance for the Measurement of Ventricular Volumes and Function in Patients with Suspected or Known Cardiac Sarcoidosis
Jason See, MBBS; Stephen Richard Underwood; Kshama Wechalekar

202b-08 Predictors of Incorporating Myocardial Blood Flow Measurements into Daily Clinical Rest/Stress Rb-82 PET Myocardial Perfusion Study Reports
Faraz Kureshi, MD, MSc; Preetham Muskula; A. Iain McGhie; Kevin Kennedy; Krishna K. Patel; Staci Courter; Mohamed Omer; James Case; Timothy Bateman

202b-09 Left Ventricular Ejection Fraction Changes Between Rest and Peak Stress by CMR: A Rb-82 Myocardial Perfusion PET Comparision Study
Preetham R. Muskula; Faraz Kureshi; Krishna K. Patel; Joseph S. Soltys; Ibrahim M. Saeed; Kevin F. Kennedy; James A. Case; Timothy M. Bateman

202b-10 Predicting the Risk for Acute Type B Aortic Intramural Hematoma by 18F-FDG PET/CT
Fan Yang, M.D.; Jianfang Luo; Qingyi Hou; Qingshan Geng

202b-11 Ratio of Myocardial Uptake to Blood Pool Activity in Dual-Time-Point 18F-FDG PET for the Diagnosis of Cardiac Sarcoidosis
Sherrie Khadanga, MD; Janusz Kikut; Sean Reynolds; Friederike K. Keating, MD; Patrick Silveira

10:00AM – 11:30AM

CA CASES WITH THE ACES

TICKETED SESSION

Session 203 Cases from the Cleveland Clinic

Location: Empire B **CME: 1.5**

Case Presenters: *Manuel D. Cerqueira, MD, MASNC; Rory Hachamovitch, MD, FASNC*

10:30AM - 12:00PM

A ADVANCED

Session 205 Imaging to Guide Arrhythmia Management

Location: New York **CME: 1.5; CE: 1.25; MOC**

Moderators: *Mario J. Garcia, MD; Hein J. Verberne, MD, PhD*

10:30AM Myocardial Remodeling Changes that Predispose to Arrhythmogenecity
Robert J. Gropler, MD, MASNC

10:45AM Radionuclide Imaging for Assessing Ventricular Arrhythmogenicity
Mark I. Travin, MD, FASNC

11:00AM Echocardiographic Assessment of Arrhythmogenicity
Mario J. Garcia, MD

11:15AM MRI Assessment of Arrhythmogenicity
Katherine C. Wu, MD

11:30AM Role of Radionuclide Imaging in Assessment of Atrial Arryhthmias
Arthur J. Scholte, MD

11:45AM Discussion

C CORE

Session 206 Nuclear Cardiology Laboratory in 2017

Location: Exhibit Hall B **CME: 1.5; CE 1.25; MOC**

Moderators: *Thomas A. Holly, MD, FASNC; David E. Winchester, MD, FASNC*

10:30AM ImageGuide: How it Can Improve Your Practice
Nishant Shah, MD, MPH

10:45AM ALARA: Practical Approaches to Radiation Reduction
James A. Case, PhD

11:00AM Laboratory Accreditation: Nuts and Bolts
Eric V. Burgett, CNMT, NCT

11:15AM Optimizing Attenuation Correction and Reconstruction
Parthiban Arumugam, MB BS

11:30AM Advances in Nuclear Camera Technology
Ernest V. Garcia, PhD, MASNC

11:45AM Discussion

MI MULTIMODALITY IMAGING

Session 207 Methods and Value of Cardiotoxicity Assessment in Oncologic Disease

Location: Atlanta **CME: 1.5; CE 1.25; MOC**

Moderators: *Jamieson M. Bourque, MD, FASNC; Saurabh Malhotra, MD, MPH, FASNC*

10:30AM Cardiac Complications of Cancer Therapy and Their Prevention and Treatment
Raymond R. Russell III, MD, PhD, FASNC

10:45AM Contemporary Radionuclide Evaluation of Oncologic Cardiotoxicity
Jamieson M. Bourque, MD, FASNC

11:00AM The Echocardiographic Approach to Assess Oncologic Cardiotoxicity
Amil M. Shah, MD

11:15AM Cardiac MRI to Evaluate Oncologic Cardiotoxicity
Michael Salerno, MD

11:30AM Case Presentations and Discussion

RE RWTE

Session 208 99mcTc-PYP Amyloid Imaging; PET for Inflammation/Infection

Location: Chicago AB **CME: 1.5; CE 1.5; MOC**

Moderators: *Dominique Delbeke, MD, PhD; Robert E. O'Donnell, MD, MPH*
Case Presenters: *Vasken Dilsizian, MD, MASNC; Edward Hulten, MD, MPH, FASNC; Edward J. Miller, MD, PhD, FASNC*

T TECHNOLOGY & TECHNIQUES

Session 209 Not Just Pushing Buttons

Location: Chicago C **CME: 1.5; CE 1.5**

Moderators: *Timothy L. Dunn, CNMT; Mark C. Hyun, CNMT, NCT, RT(N)(R), FASNC*

10:30AM Acquisition Parameters (Conventional and Solid State)
Jaime Warren, CNMT, MBA

11:00AM Processing Parameters (Conventional and Resolution Recovery)
Marie F. Kijewski, ScD

11:30AM Types of Filters and Their Parameters
Mi-Ae Park, PhD

12:00PM - 1:30PM

CA CASES WITH THE ACES

TICKETED SESSION

Session 210 Cases from St. Luke's Roosevelt Hospital/Mt. Sinai School of Medicine

Location: Empire B **CME: 1.5**

Case Presenter: *E. Gordon DePuey, MD, MASNC*

12:15PM – 1:15PM

O OTHER

Session 211 Ethics in Nuclear Cardiology: A Focus on Informed Consent

Location: Chicago AB **CME: 1.0**

Podium Moderator: *Andrew J. Einstein, MD, PhD, FASNC*
Audience Moderators: *Matthew Parker, MD; Gregory S. Thomas, MD, MPH, MASNC*
Panelists: *Stephen A. Bloom, MD, FASNC; Ronald G. Schwartz, MD, FASNC; Leslee J. Shaw, PhD, MASNC*

12:15PM Patient Centered Imaging: A Background Presentation on Shared Decision Making
Leslee J. Shaw, PhD, MASNC

12:25PM Frequent MUGA Testing in a Myeloma Patient: Case-based
Sabha Bhatti, MD, FASNC

12:30PM Panel and Audience Discussion

12:50PM Consenting Inappropriate Patients: Case-based
Matthew E. Harinstein, MD, FASNC

12:55PM Panel and Audience Discussion

Friday, September 15 (cont.)

1:30PM – 3:00PM

PL PLENARY

Session 215 Multimodality Imaging in the Diagnosis and Management of Heart Failure

Location: Exhibit Hall B **CME: 1.5; CE: 1.25; MOC**

Moderators: *James E. Udelson, MD, MASNC; Mary N. Walsh, MD, FASNC*

1:30PM How Does Imaging Guide Contemporary Management of the Heart Failure Patient?
Mary N. Walsh, MD, FASNC

1:45PM Evaluation of Ischemia and Viability in Heart Failure/LV Dysfunction: Is it Still Relevant?
Gary R. Small, MD

2:00PM Novel Approaches to Evaluate Myocardial Inflammatory Diseases
Ron Blankstein, MD, FASNC

2:15PM The Rapidly Emerging Role of Multimodality Imaging to Diagnose and Manage the Cardiac Amyloidoses
Frederick L. Ruberg, MD

2:30PM Patient Perspective: Experiencing a Heart Transplant (An Interview)
Rory Hachamovitch, MD, FASNC

2:50PM Discussion

T TECHNOLOGY & TECHNIQUES

Session 216 Patients are Different — So are Protocols

Location: Chicago C **CME: 1.5; CE: 1.5**

Moderators: *Robert A. Pagnanelli, CNMT, RT(N)(R), NCT, FASNC; Jaime Warren, CNMT, MBA*

1:30PM BMI-Based Dosing
Robert A. Pagnanelli, CNMT, RT(N)(R), NCT, FASNC

2:00PM Stress First or Rest First?
John J. Mahmarian, MD, MASNC

2:30PM Pharmacologic Stress Agents — Which is the Best for my Patient?
Matthew Parker, MD

3:00PM – 4:30PM

CA CASES WITH THE ACES

TICKETED SESSION

Session 217 Cases from MMP MaineHealth Cardiology

Location: Empire B **CME: 1.5**

Case Presenters: *Mylan C. Cohen, MD, MPH, MASNC; Waseem Chaudhry, MD*

3:00PM – 4:00PM

AR ABSTRACTS/RESEARCH

Session 218a ePosters: Advances in PET Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Timothy M. Bateman, MD, MASNC*

3:05PM 218a-01 Ability of Quantitative Blood Flow Analysis of 13NH3 PET to Predict High Risk Coronary Disease
Waddy Gonzalez, MD, MD; Piotr Slomka, PhD; Lili Zhang, MD, ScM; Na Song, PhD; Sanford Abramson, PA; Veronica Francois, NP; Mark Travin, MD

3:15PM 218a-02 Effect of Exercise and Regadenoson Stress on Peak Hyperemic Myocardial Blood Flow and Coronary Flow Reserve in Healthy Subjects
Yin Ge, MD; Sophia Jacob; David Yang; Karla Sirianni; William Sticka; Jon Hainer; Marcelo DiCarli; Sharmila Dorbala

3:25PM 218a-03 Detection of Myocardial Inflammation by T2-weighted Imaging on Cardiac MRI versus FDG PET Among Patients with Suspected Cardiac Sarcoidosis
Paco E. Bravo, MD; Tomas S. Vita; Viviany Taqueti; Mahdi Veillet-Chowdhury; Michael Steigner; Hicham Skali; Sharmila Dorbala; Marcelo F. Di Carli; Ron Blankstein

3:35PM 218a-04 Effect of Exercise and Regadenoson Stress on Peak Hyperemic Myocardial Blood Flow and Coronary Flow Reserve in Clinical Subjects
Yin Ge, MD; Sophia Jacob; Karla Sirianni; David Yang; William Sticka; Jon Hainer; Marcelo DiCarli; Sharmila Dorbala

3:45PM 218a-05 Quantification of Right Ventricular Function Using PET: Comparison with Cardiac Magnetic Resonance
Krasimira M. Mikhova, MD; Keri M. Hiller; James R. Corbett; Edward P. Ficaro; Venkatesh L. Murthy

AR ABSTRACTS/RESEARCH

Session 218b Posters: New Techniques in Myocardial Perfusion Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Ernest V. Garcia, PhD, MASNC*

218b-12 Detection of Dynamic PET Data Technical Problems by Automated Quality Control Algorithms
Andrew Van Tosh, M.D.; Jaison J. Mathew; John R. Votaw; C. David Cooke; Christopher J. Palestro; Kenneth J. Nichols, PhD

218b-13 Efficacy of β-blocker in Patients with Hypertension plus Atrial Fibrillation Assessed by Metaiodobenzylguanidine Imaging
Masahiko Nakamura, Ph.D; Tomoko Harama; Yu Murata; Takuya Shimizu; Toshiaki Yano; Aritaka Makino; Ken Umetani; Keita Sano; Kenichi Watanabe

218b-14 Temporal Changes and Mechanism of Left Ventricular Dyssynchrony Early After Acute Myocardial Infarction Assessed by SPECT MPI: An Experimental Study
Feifei Zhang; Yuetao Wang, MD; Xiaoliang Shao; Jianfeng Wang

218b-15 Left Ventricular Mass Significantly Affects Left Ventricular Volume Measurement Using D-SPECT: A Comparison with Echocardiography
Jose Ricardo Po, MD; Alekhya Potluri; John Rehder; Mark Doyle; Indu Poornima

218b-16 Early Dynamic Evolution of Left Ventricular Remodeling and its Correlative Factors After Acute Myocardial Infarction Assessed by Gated SPECT
Wei Yang; Yuetao Wang, MD; Jianfeng Wang; Xiaoliang Shao

218b-17 Pharmacologic Stress Testing after Suboptimal Exercise Performance
William L. Hiser, MD; Dev Basu; Hari Pokharel; Paul F. Visintainer

218b-18 **Synchrony Analysis and Activation Sequences of the Left Ventricle in Patients with Left Bundle Branch Block**
Juan Erriest Sr., MD; Monica Redolatti; Gustavo Vigo; Victor Arregui; Luis Cartasegna; Luis Castro; Maria Laura Plastino; Alejandro Vilchez; Javier Moreno; Erick Alexanderson; Jorge Camilletti

218b-19 **A Case of Prolonged Ventricular Standstill Following Regadenoson Injection With Incidental Late Gadolinium Enhancement on Cardiac MRI**
Laith Derbas, MD; Abdul-rahman Abdel-karim; Ibrahim M. Saeed; A. Iain McGhie; Timothy M. Bateman

218b-20 **Novel SPECT-MPI Parameters as Predictors of Obstructive Coronary Artery Disease**
Giorgio A. Medranda, MD; Anjili Srivastava; Connor Healey; Kevin Marzo; Joshua Deleon; Zack Williams; Rose Calixte; Beevash Ray

218b-21 **Cardiac Amyloidosis Presenting with Recurrent Syncope and Diagnosed Following Exercise SPECT Myocardial Perfusion Imaging**
Ji Can Yang; Mena Yacoub, DO; Michael Youssef; John Makaryus

4:00PM – 5:30PM

MI MULTIMODALITY IMAGING

Session 221 Evaluation of Suspected Coronary Artery Disease in Women: A Comparison of the Different Imaging Modalities

Location: New York **CME: 1.5; CE: 1.25; MOC**

Moderator: *Regina S. Druz, MD, FASNC; Lawrence M. Phillips, MD, FASNC*

4:00PM Challenges in the Evaluation of Heart Disease in Women
Gary V. Heller, MD, PhD, MASNC

4:15PM In Women, Anatomic Imaging with CT is Preferred
Kavitha Chinnaiyan, MD

4:30PM In Women, Functional Imaging with Radionuclide Imaging is Better
Viviany R. Taqueti, MD

4:45PM In Women, Functional Imaging with CMR is Better
Balaji K. Tamarappoo, MD, PhD

5:00PM Case Presentations and Discussion

P PET

Session 222 How to Establish a Cardiac PET Program

Location: Exhibit Hall B **CME: 1.5; CE: 1.25; MOC**

Moderators: *Erick Alexanderson, MD; Raymond R. Russell III, MD, PhD, FASNC*

4:00PM Which Business Model is Right for my Practice?
Timothy M. Bateman, MD, MASNC

4:20PM Start-up Considerations and Patient Selection for Cardiac PET
Mouaz H. Al-Mallah, MD, FASNC

4:40PM Workflow Strategies in a Cardiac PET Program
Ritesh Dhar, MD

5:00PM PET Perfusion Tracers: Which One to Choose for Which Model
Gary V. Heller, MD, PhD, MASNC

5:20PM Discussion

RE RWTE

Session 223 Appropriate Use of Nuclear Stress Imaging

Location: Chicago AB **CME: 1.5; CE: 1.5; MOC**

Moderators: *Robert C. Hendel, MD, MASNC; Todd D. Miller, MD*

Case Presenters: *Renee Bullock-Palmer, MD, FASNC; Thomas A. Holly, MD, FASNC; Vikas Veeranna, MD*

T TECHNOLOGY & TECHNIQUES

Session 224 RWTE for Technologists

Location: Chicago C **CME: 1.5; CE: 1.5**

Moderators: *Joseph Dietz, CNMT; Robert A. Pagnanelli, CNMT, RT(N)(R), NCT, FASNC*

4:00PM Myocardial Perfusion Imaging Artifacts — Could I Have Prevented That?
Eric J. Schockling, CNMT

4:30PM Solid State (530c/DSPECT) Cases
Ronald G. Schwartz, MD, FASNC

5:00PM Conventional Cases
E. Gordon DePuey, MD, MASNC

4:00PM – 5:00PM

I INTERNATIONAL

Session 225 International Atomic Energy Agency Global Initiatives - Part 1

Location: Atlanta **CME: 1.0; CE: .75**

Moderators: *Nathan Better, MB BS; Felix Keng, MD, FASNC*

4:00PM The IAEA Nuclear Cardiology Protocols Study (INCAPS): Building Research Collaborations Between ASNC and IAEA
Andrew J. Einstein, MD, PhD, FASNC

4:20PM The Challenges to Develop Nuclear Cardiology with Competing Modalities in the Developing World
Joao Vitola, MD, PhD

4:40PM Discussion

5:15PM – 6:15PM

I INTERNATIONAL

Session 226 International Atomic Energy Agency Global Initiatives - Part 2

Location: Atlanta **CME: 1.0; CE: .75**

Moderators: *Nathan Better, MB BS; Felix Keng, MD, FASNC*

5:15PM Case Presentation: The Present Status of Medical Radiation and Nuclear Medicine Usage in Japan
Takashi Kudo, MD, PhD

5:35PM Case Presentation: Revascularization Predicts Improved Prognosis in Egyptian Patients with Stable CAD and Large Ischemic Perfusion Defects
Adel H. Allam, MD, FASNC

5:55PM Discussion

Saturday, September 16

6:30AM - 7:45AM

O OTHER

Session 300 ImageGuide Registry Informational Session

Location: Chicago C

Additional information can be found on page ??

7:55AM - 9:30AM

PL PLENARY

Session 301 The Emerging Clinical Challenge of Symptomatic Non-obstructive Coronary Artery Disease

Location: Exhibit Hall B **CME: 1.5; CE 1.25; MOC**

Moderators: *John Wells Askew, MD, FASNC; Randall C. Thompson, MD, FASNC*

7:55AM Recognition of New FASNC and MASNC Members and JNC Award Recipients
Randall C. Thompson, MD, FASNC and Ami E. Iskandrian, MD, PhD, MASNC

8:00AM Nomenclature: Syndrome X, Microvascular Angina, Coronary Microvascular Dysfunction — One and the Same?
Leslee J. Shaw, PhD, MASNC

8:20AM Is This the Sweet Spot for Coronary CT?
Daniel S. Berman, MD, MASNC

8:40AM The Challenge with Stress Testing: How to Differentiate Microvascular Disease from a False Positive Test
Raymond J. Gibbons, MD, MASNC

9:00AM Can Imaging Help Guide Management?
Viviany R. Taqueti, MD

9:20AM Discussion

9:30AM – 9:45AM
ASNC Annual Business Meeting
Location: Exhibit Hall B

9:30AM - 10:30AM

AR ABSTRACTS/RESEARCH

Session 302a ePosters: New Techniques in Myocardial Perfusion Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Renee Bullock-Palmer, MD, FASNC*

9:35AM 302a-01 Usefulness of Quantitative Assessment of Myocardial Blood Flow With D-SPECT in Patients With Multivessel Coronary Artery Disease: Comparison With Visual Qualitative Assessment
Emi Tateishi; Keisuke Kiso; Hayato Hosoda; Yasuhide Asaumi; Tetsuya Fukuda

9:45AM 302a-02 The Prognostic Value of Heart Rate Response During Vasodilator Stress Myocardial Perfusion Imaging in Patients with End Stage Renal Disease Undergoing Renal Transplantation
Ibtihaj Fughhi; Chiedozie Anokwute; Tania Campagnoli; Marwan Wassouf; Michael Kharouta; Aviral Vij; Andrew Appis; Amjad Ali; Wael Aljaroudi; Rami Doukky

9:55AM 302a-03 Improved Quantitative SPECT Myocardial Uniformity of Myocardial Uptake Using a Half-Time, Iterative Resolution Recovery Algorithm.
James A. Case, PhD; Jessica Jensen; Staci A. Courter; Paul Helmuth; Timothy M. Bateman

10:05AM 302a-04 Assessment of Coronary Calcium Score Using Integrated PET Myocardial Perfusion Quantitative Software Method: Comparison With the Standard Stand Alone Software Systems
Mark C. Hyu; Frances Wang; Heidi Gransar; Norman Gellada; Serge D. VanKriekinge; Piotr Slomka; Damini Dey; Parker Waechter; Sean W. Hayes; Louise E. Thomson; John D. Friedman; Daniel S. Berman

10:15AM 302a-05 Combined Echocardiography and Pyrophosphate Imaging Detect Cardiac Amyloidosis with High Accuracy Among Elderly with Aortic Stenosis
Vasvi Singh, MD; Clark Zhang; Saurabh Malhotra

AR ABSTRACTS/RESEARCH

Session 302b Posters: New Developments in Quality and Appropriate Imaging

Location: Exhibit Hall A **CME: 1.0**

Abstract Discussant: *Alia Abdel Fattah, MD, FASNC*

302b-22 The Impact of Initial Myocardial Perfusion Imaging vs. Invasive Coronary Angiography on Outcomes of Coronary Artery Disease: A Nationwide Cohort Study
Guang-Uei Hung, MD

302b-23 Sensitivity of 8-Frame Cadmium-Zinc-Telluride Single Photon Emission Computed Tomography for the Assessment of Diastolic Dysfunction
Ji Can Yang, DO; Nicholas Chan; Badewattie Narine; John Makaryus; Joseph Diamond

302b-24 Prognostic Value of LV Diastolic Dyssynchrony from SPECT MPI in Patients with DCM
Dianfu Li; Cheng Wang; Haipeng Tang; Guang-Uei Hung; Weihua Zhou, PhD

302b-25 A Comparison of Left Ventricular Volumes and Ejection Fraction by Various Commercially Available Nuclear Cardiology Software on a CZT SPECT Camera
Chad M. House, BS, RDCS, FASE; Kelly S. Root; Jill C. Schreiner; Patricia K. Turnquist; Katie A. Moriarty; William B. Nelson

302b-26 How Soon is Now? Delay in the Utilization of Technetium-99m Pyrophosphate Scintigraphy for the Diagnosis of Cardiac Transthyretin Amyloidosis in Patients with Symptoms
Nikolaos Papoutsidakis, MD, PhD; Daniel Jacoby; Anna Rodonski; Edward Miller

302b-27 A Phantom Study of Positional Change in Defect Size And Severity: Is Everything That Moves Really an Artifact?
Aaron M. Timins, DO; Mark Task; Andrew Althouse; Matthew E. Harinstein; Prem Soman

302b-28 Clinical feasibility of Adenosine Stress Lung Thallium-201 Uptake in Patients With Pulmonary Congestive Heart Failure
Hiroyuki Namura, MD

302b-29 Preliminary Analysis of Previously Undescribed D-SPECT Nuclear Camera Artifact
Matthew D. Roby, D.O.; Matthew M. Schumaecker; Melanie Spangler; Jacek S. Slowikowski

302b-30 Quantitative Myocardial Perfusion and Flow Distribution in Human with 99mTc-Tetrofosmin Dynamic Cardiac SPECT
Uttam M. Shrestha, PhD; Maria Sciammarella; Youngho Seo; Grant Gullberg; Elias Botvinick

302b-31 Contribution of Coronary Artery Calcification in the Prediction of Diastolic Dysfunction Parameters as Assessed by Myocardial Perfusion SPECT
Lakshmi Subramanian, MBBCh BAO; William Vezina; Jonathan Romsa; Cigdem Akincioglu; Rob Stodilka; James Warrington

10:00AM - 11:30AM

CA CASES WITH THE ACES

TICKETED SESSION

Session 303 Cases from Brigham & Women's Hospital

Location: Empire B **CME: 1.5**

Case Presenters: *Sharmila Dorbala, MD, FASNC; Marcelo Di Carli, MD; Vikram Agarwal, MD, MPH*

10:30AM - 12:00PM

A ADVANCED

Session 304 Cutting Edge Technologies

Location: New York **CME: 1.5; CE: 1.25; MOC**

Moderators: *Renee Bullock-Palmer, MD, FASNC; Indu Poornima, MD*

10:30AM Latest in SPECT and PET Hardware Development
Piotr J. Slomka, PhD

10:50AM New Tracers on the Horizon
Mehran Sadeghi, MD

11:10AM Theranostics — Wave of the Future
Albert J. Sinusas, MD, FASNC

11:30AM Kinetic Remodeling: What You Need to Know to Obtain Reliable Quantitative Flow
Robert A. deKemp, PhD

11:50AM Discussion

C CORE

Session 305 Cardiac Amyloidosis in 2017

Location: Exhibit Hall B **CME: 1.5; CE 1.25 MOC**

Moderators: *Mylan C. Cohen, MD, MPH, MASNC; Paul Cremer, MD*

10:30AM Pathogenesis of Amyloidosis
Kevin M. Alexander, MD

10:50AM What's New and What's on the Horizon in Diagnosis and Treatment
Frederick L. Ruberg, MD

11:10AM Echocardiography and MRI in Amyloidosis
Edward Hulten, MD, MPH, FASNC

11:30AM Common and Uncommon Findings of PYP Imaging with Cases
Sabahat Bokhari, MD, FASNC

11:50AM Discussion

P PET

Session 306 Imaging in Sarcoidosis (Update on Guidelines): A Joint Session with the Society of Nuclear Medicine and Molecular Imaging

Location: Atlanta **CME: 1.5; CE 1.25; MOC**

Moderators: *Ron Blankstein, MD, FASNC; Robert J. Gropler, MD, MASNC*

10:30AM Imaging in Unexplained Cardiomyopathy: A Clinician's Perspective
Leslie T. Cooper, MD

10:50AM Non-invasive Imaging for Cardiac Sarcoidosis: the European Perspective
Hein J. Verberne, MD, PhD

11:10AM PET/CT for Detection and Management of Sarcoidosis: Update from the New Guidelines
Panithaya Chareonthaitawee, MD

11:30AM What's Next for Imaging to Direct Therapy in Cardiac Sarcoidosis: Current and Future Approaches
David Birnie, MD

11:50AM Discussion

RE RWTE

Session 307 Imaging for the Detection or Risk Assessment of Stable Coronary Artery Disease: Get with the Guidelines

Location: Chicago AB **CME: 1.5; CE 1.5; MOC**

Moderators: *Rami Doukky, MD, FASNC; Nishant Shah, MD, MPH*

Case Presenters: *Rami Doukky, MD, FASNC; Myron C. Gerson, MD, MASNC*

T TECHNOLOGY & TECHNIQUES

Session 308 Cardiac PET: Focus on Myocardial Perfusion Imaging

Location: Chicago C **CME: 1.5; CE 1.5**

Moderators: *Timothy L. Dunn, CNMT; Eric J. Schockling, CNMT*

10:30AM Acquisition/Processing Parameters
Mi-Ae Park, PhD

11:00AM Radiation Reduction in PET
James A. Case, PhD

11:30AM PET (CIED Infection, Prosthetic Valve Endocarditis, Sarcoidosis)
Hicham Skali, MD

Saturday, September 16 (cont.)

12:00PM - 1:30PM

CA CASES WITH THE ACES

TICKETED SESSION

Session 310 Cases from Brown University

Location: Empire B **CME: 1.5**

Case Presenters: *Brian G. Abbott, MD, MASNC; James A. Arrighi, MD, MASNC; Raymond R. Russell III, MD, PhD, FASNC; Nishant Shah, MD*

1:30PM - 3:00PM

A ADVANCED

Session 315 Debate: Clash of the Titans

Location: Exhibit Hall B **CME: 1.5; CE 1.5; MOC**

Moderators: *Lawrence M. Phillips, MD, FASNC; L. Samuel Wann, MD*

1:30PM Is Solid State SPECT a Viable Substitute for PET Imaging? PRO
Prem Soman, MD, PhD, FASNC

1:40PM Is Solid State SPECT a Viable Substitute for PET Imaging? CON
Terrence D. Ruddy, MD

1:50PM Rebuttals

2:00PM Is CT-FFR Assessment Offlow Physiology Comparable to PET? PRO
Benjamin Chow, MD, FASNC

2:10PM Is CT-FFR Assessment Offlow Physiology Comparable to PET? CON
K. Lance Gould, MD

2:20PM Rebuttals

2:30PM Is CT Attenuation Correction the Best Option for PET Imaging? PRO
Marcelo Di Carli, MD

2:40PM Is CT Attenuation Correction the Best Option for PET Imaging? CON
Nils P. Johnson, MD

2:50PM Rebuttals

C CORE

Session 316 Patient Centered Myocardial Perfusion Imaging

Location: New York **CME: 1.5; CE 1.25; MOC**

Moderators: *Jeffrey A. Leppo, MD, MASNC; Peter Tilkemeier, MD, FASNC*

1:30PM Appropriate Use: Are We Making Progress?
Robert C. Hendel, MD, MASNC

1:50PM Personalized Protocol Selection
W. Lane Duvall, MD

2:10PM Optimizing the Clinical Value of Reports
Peter Tilkemeier, MD, FASNC

2:30PM Current Health Policy Issues: Implications for Patient Choice and Costs
William A. Van Decker, MD, MASNC

2:50PM Discussion

P PET

Session 317 How to Incorporate PET Myocardial Blood Flow Quantification into Practice

Location: Atlanta **CME: 1.5; CE 1.25; MOC**

Moderators: *Thomas H. Schindler, MD; Edward J. Miller, MD, PhD, FASNC*

1:30PM Why Is it Important?
Thomas H. Schindler, MD

1:50PM Practical Image Acquisition/Processing
Robert A. deKemp, PhD

2:10PM Optimizing PET Interpretation and Reporting: Incorporating MPI, MBF, CAC and More
Edward J. Miller, MD, PhD, FASNC

2:30PM How to Incorporate Flow Measurements (Beyond MPI and CAC) to Direct Patient Care
Parthiban Arumugam, MB BS

2:50PM Discussion

RE RWTE

Session 318 Viability Assessment (SPECT and PET)

Location: Chicago AB **CME: 1.5; CE 1.5; MOC**

Moderators: *Thomas A. Holly, MD, FASNC; Ami E. Iskandrian, MD, PhD, MASNC*

Case Presenters: *Paul Cremer, MD; Jamshid Maddahi, MD, FASNC; Hein J. Verberne, MD, PhD*

T TECHNOLOGY & TECHNIQUES

Session 319 Nuclear Cardiology Beyond Plain Myocardial Perfusion Imaging

Location: Chicago C **CME: 1.5; CE 1.5**

Moderators: *Eric J. Schockling, CNMT*

1:30PM PYP Imaging in Amyloidosis: Acquisition and Quantitation
Sabahat Bokhari, MD, FASNC

2:00PM Myocardial Blood Flow with SPECT: Acquisition and Quantitation
Mark C. Hyun, CNMT, NCT, RT(N)(R), FASNC

2:30PM Translational Tracers for Nuclear Cardiology
Albert J. Sinusas, MD, FASNC

3:00PM - 4:30PM

CA CASES WITH THE ACES

TICKETED SESSION

Session 321 Cases from Mayo Clinic

Location: Empire B **CME: 1.5**

Case Presenters: *Panithaya Chareonthaitawee, MD; Todd D. Miller, MD*

3:15PM - 4:15PM

O OTHER

Session 322 Choosing Wisely Challenge

Location: New York

Additional Information can be found on page ??

4:00PM - 5:30PM

P PET

Session 325 New Directions in Cardiovascular PET: A Joint Session with the European Association of Nuclear Medicine

Location: Atlanta **CME: 1.5; CE 1.25; MOC**

Moderators: *Fabien Hyafil, MD, PhD; Terrence D. Ruddy, MD*

4:00PM PET vs. MR (and PET/MR) for Ischemic and Non-ischemic Cardiomyopathy
Robert J. Gropler, MD, MASNC

4:20PM New Approaches to Molecular Imaging with PET
Hein J. Verberne, MD, PhD

4:40PM Role of PET in Valvular Disease
Fabien Hyafil, MD, PhD

5:00PM Role of PET in Transplant Vasculopathy
Sharon Chih, MBBS, PhD

5:20PM Discussion

RE RWTE

Session 326 New Technology in SPECT (Attenuation Correction, CZT)

Location: Chicago AB **CME: 1.5; CE 1.5; MOC**

Moderators: *James A. Arrighi, MD, MASNC; Alia Abdel Fattah, MD, FASNC*
Case Presenters: *W. Lane Duvall, MD; Edward J. Miller, MD, PhD, FASNC*

T TECHNOLOGY & TECHNIQUES

Session 328 Multimodality Imaging

Location: Chicago C **CME: 1.5; CE 1.5**

Moderators: *Maria Costello, CNMT; Haresh Majmundar, CNMT, RT(N)*

4:00PM Cardiac CT
Mark C. Hyun, CNMT, NCT, RT(N)(R), FASNC

4:30PM Echocardiography
Dennis A. Calnon, MD, MASNC

5:00PM Cardiac MRI
Balaji K. Tamarappoo, MD, PhD

4:30PM - 5:30PM

AR ABSTRACTS/RESEARCH

Session 327 Featured Research Oral Abstracts

Location: New York **CME: 1.0; CE: 1.0**

Moderators: *Maria G. Sciammarella, MD; Manuel D. Cerqueira, MD, MASNC*

4:30PM 327-01 The Prognostic Value of Ischemic ECG Changes in Patients Undergoing Regadenoson Stress Myocardial Perfusion Imaging
Rami Doukky, MD, FASNC; Ibtihaj Fughhi; Rozi Khan; Chiedozie Anokwute; Ali Ayoub; Snigdha Kola; Mina Iskander; Fady Iskander; Mark Sahyouni; Bala Hota

4:42PM 327-02 Association of Nuclear Cardiology Laboratory Accreditation with Downstream Resource Utilization and Clinical Outcomes
Venkatesh L. Murthy, MD, PhD; Jessica Lehrich; Ravi V. Shah; Hong J. Yun; James R. Corbett; Edward P. Ficaro; Rory Hachamovitch; Leslee J. Shaw; Brahmajee K. Nallamothu

4:54PM 327-03 Left Ventricular Ejection Fraction Reserve Derived with PET, but not SPECT, Myocardial Perfusion Imaging Predicts Presence of Multivessel Coronary Artery Disease by Coronary Angiography: Same-Patient, Head-to-head PET vs. SPECT Comparison
Firas Al Badarin, MD; Timothy Bateman; Staci Courter

5:06PM 327-04 Direct Comparison Between Relative 18F-fluorodeoxyglucose Uptake and Late Gadolinium Enhancement on Cardiac MRI by Using PET/MRI
Atsuro Masuda, MD, PhD; Ayaka Nemoto; Noboru Oriuchi; Hiroshi Ito; Yasuchika Takeishi

5:18PM 327-05 Development of a Simple Screening Measure to Approximate Resting Myocardial Blood Flow in Rb-82 PET: Value of the Rate-pressure Product
Mohamed Omer, MD; Faraz Kureshi; Preetham Muskula; Krishna K. Patel; Kevin Kennedy; Ibrahim Saeed; Staci Courter; James A. Case; Timothy M. Bateman

5:45PM - 6:45PM

AR ABSTRACTS/RESEARCH

Session 330 Young Investigator Competition

Location: Chicago C **CME: 1.0; CE: 1.0**

Moderator: *Gary V. Heller, MD, PhD, MASNC*
Judges: *Fadi G. Hage, MD, FASNC; Rami Doukky, MD, FASNC; Barry L. Zaret, MD, MASNC; James A. Case, PhD*

5:45PM 330-01 A Novel Matrix Metalloproteinase Targeting Tracer for PET Imaging of Aneurysms
Jakub Toczek, PhD; Yunpeng Ye; Kiran Gona; Jiasheng Zhang; Jinah Han; Jae-Joon Jung; Mehran M. Sadeghi

5:57PM 330-02 Accuracy of the Non-invasive Diagnosis of Cardiac Amyloidosis: A Multi-modality Registry Analysis
Ahmad Masri, MD; Ricardo Nieves; Islam Abdelkarim; Michael S. Sharbaugh; Andrew D. Althouse; William Follansbee; Joao L. Cavalcante; Timothy Wong; Erik B. Schelbert; Prem Soman

6:09PM 330-03 Intracellular Behavior of the Novel Sympathetic Nerve Agent 18F-LMI1195
Rudolf A. Werner, MD; Xinyu Chen; Constantin Lapa; Simon Robinson; Takahiro Higuchi

6:21PM 330-04 Head-to-head Comparison of SPECT- and PET-Derived Stress Left Ventricular Functional Measurements Using Same-Patient, Near-Simultaneous PET and SPECT Acquistions
Firas Al Badarin, MD; Timothy Bateman; Staci Courter

6:33PM 330-05 Analysis of Raw Polar Maps from Myocardial Perfusion SPECT by Gender-adjusted Deep Learning Improves Automatic Prediction of Obstructive Coronary Disease
Julian A. Betancur, PhD; Frederic Commandeur; Tali Sharir; Mathews Fish; Terrence Ruddy; Philipp Kaufmann; Timothy Bateman; Sharmila Dorbala; Guido Germano; Daniel Berman; Damini Dey; Piotr Slomka

Sunday, September 17

8:00AM - 9:30AM

PL PLENARY

Session 401 Controversies in Clinical Cardiology and Cardiac Imaging

Location: Atlanta **CME: 1.5; CE 1.5; MOC**

Moderators: *Prem Soman, MD, PhD, FASNC; Viviany R. Taqueti, MD*

8:00AM Debate 1 - Breakthrough: Novel approaches for Early Detection of Chemotherapy Cardiotoxicity
W. Gregory Hundley, MD

8:12AM Debate 1 - Controversy: What Would it take for Novel Markers of Cardiac Toxicity to Replace Ejection Fraction
Indu Poornima, MD

8:24AM Discussion

8:30AM Debate 2 - Breakthrough: FDG Imaging of Cardiac and Vascular Inflammation
Ahmed Tawakol, MD

8:42AM Debate 2 - Controversy: Is FDG Imaging the Be-all and End-all?
Robert J. Gropler, MD, MASNC

8:54AM Discussion

9:00AM Debate 3 - Breakthrough: Noninvasive Quantification of Coronary Flow Reserve
Marcelo Di Carli, MD

9:12AM Debate 3 - Controversy: Is Coronary Flow Reserve Good Enough to Guide Management in Coronary Artery Disease?
K. Lance Gould, MD

9:24AM Discussion

9:45AM - 10:45AM

A ADVANCED

Session 402 Approach to Known or Potential Ischemic Heart Disease

Location: Atlanta **CME: 1.0; CE 1.0; MOC**

Moderators: *Justin B. Lundbye, MD, FASNC; Mark I. Travin, MD, FASNC*

9:45AM Which Imaging Test to Begin within the Context of Varying Guidelines
Manuel D. Cerqueira, MD, MASNC

10:00AM Benefits of Myocardial Blood Flow Quantitation (with Attention to Microvascular Disease, Especially in Women)
Venkatesh L. Murthy, MD, PhD

10:15AM Imaging Plaque: How do We do It?
Mehran Sadeghi, MD

10:30AM Radionuclide Imaging of Peripheral Arterial Disease
Mitchel R. Stacy, PhD

RE RWTE

Session 403 PET Perfusion/Myocardial Blood Flow

Location: Chicago AB **CME: 1.0; CE 1.0; MOC**

Moderators: *Karthikeyan Ananthasubramaniam, MD, FASNC; Thomas H. Schindler, MD*

Case Presenters: *Dennis A. Calnon, MD, MASNC; Viviany R. Taqueti, MD*

11:00AM - 12:00PM

C CORE

Session 404 How Does Radionuclide Imaging Guide Clinical Decision Making?

Location: Atlanta **CME: 1.0; CE 1.0; MOC**

Moderators: *Christopher L. Hansen, MD, FASNC; Hicham Skali, MD*

11:00AM How to Decide When to Proceed to Angiography
Hicham Skali, MD

11:20AM Latest in Viability Assessment
Jamshid Maddahi, MD, FASNC

11:40AM Preoperative Testing: When is Preoperative Evaluation Helpful
Todd D. Miller, MD

MI MULTIMODALITY IMAGING

Session 405 Multimodality Assessment of Complex Cardiovascular Disease

Location: Chicago AB **CME: 1.0; CE 1.0; MOC**

Moderators: *Ibrahim M. Saeed, MD; Joao Vitola, MD, PhD*

11:00AM A Patient with Chest Pain and an Anomalous Coronary Artery
Steven C. Port Jr., MD

11:15AM A Patient with Ischemic Cardiomyopathy and Heart Failure
Ibrahim M. Saeed, MD

11:30AM A Patient with Pocket Erythema and Swelling Post-ICD Placement
Vasken Dilsizian, MD, MASNC

11:45AM A Patient with Peripheral Arterial Disease
Randall C. Thompson, MD, FASNC

ASNC's International Association Partners

- International Atomic Energy Agency (IAEA)
- AOFNMB (Asia Oceania Federation of Nuclear Medicine and Biology)
- ALASBIMN (Latin American Association of Biology and Nuclear Medicine)
- Argentine Federation of Cardiology
- Brazilian Society of Cardiology
- Chinese Society of Nuclear Medicine
- Egyptian Society of Cardiology
- European Association of Nuclear Medicine
- European Society of Cardiology
- Inter-American Society of Cardiology
- Japanese Society of Nuclear Cardiology
- Japanese Society of Nuclear Medicine
- Kuwait Society of Nuclear Medicine
- Mexican Society of Cardiology
- Saudi Heart Association
- Spanish Society of Nuclear Medicine and Molecular Imaging
- Turkish Society of Cardiology
- Turkish Society of Nuclear Medicine
- World Federation of Nuclear Medicine and Biology

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General Information

Americans with Disabilities Act:

ASNC supports the Americans with Disabilities Act and will be glad to assist you with any special needs to make this program accessible to you.

Admission Requirements

Admission to all sessions and the exhibit hall is by badge only.

ASNC Booth

Located outside outside the Expo Hall.

ASNC2017 Meeting on Demand

All attendees can obtain access to the ASNC2017 MOD by visiting the Astellas booth on the expo floor to obtain an access code. This is a non-CME product. Information about purchasing a CME MOD will be provided to all attendees by email. Corporate support for the non-CME access is provided by Astellas Pharma US, Inc.

Coat and Baggage Check

ASNC does not provide coat or baggage check. Bags may be checked at the bell stand in the hotel lobby.

Mobile App

Please go to page 25 in this program to view download instructions for the ASNC2017 mobile app.

Mobile Phones, Pagers, Other Electronic Devices

For consideration of others, please remember to silence all electronic devices while in educational sessions.

No Smoking Policy

Smoking is prohibited in all meeting spaces of the Sheraton Kansas City Crown Center. Your compliance is appreciated.

Speaker Ready Room

ASNC requests that faculty use the audio-visual equipment in the speaker ready room to prepare presentations. The Speaker Ready room is located in Chouteau A on the Mezzanine Level of the Sheraton. The room will be staffed with technicians to assist faculty:

Thursday, September 14, 2017	10:00 a.m. – 5:00 p.m.
Friday, September 15, 2017	7:00 a.m. – 4:00 p.m.
Saturday, September 16, 2017	7:00 a.m. – 4:00 p.m.
Sunday, September 17, 2017	7:00 a.m. – 10:00 a.m.

WiFi Available

Wifi is available in the Education rooms and public areas of the Sheraton. Corporate support for Wifi is provided by Astellas Pharma US, Inc.

Access Wifi by entering: Username: ASNC2017
Password: astellas

Facebook: facebook.com/myasnc | Twitter: @myasnc | #ASNC2017

Exhibitor Listing

Exhibit Hall Hours

Thursday, September 14, 2017

6:00 p.m. – 7:30 p.m. Welcome Reception and Exhibit Hall Grand Opening

Friday, September 15, 2017

9:30 a.m. – 4:30 p.m.

9:30 a.m. – 10:30 a.m. Refreshment Break in the Exhibit Hall

3:00 p.m. – 4:00 p.m. Beer and Pretzels Happy Hour in the Exhibit Hall

Saturday, September 16, 2017

9:30 a.m. – 3:00 p.m.

9:30 a.m. – 10:30 a.m. Refreshment Break in the Exhibit Hall

The ASNC Exhibit Hall is a one-of-a-kind marketplace to visit and explore the latest offerings in nuclear cardiology. ASNC attendees meet face-to-face with industry leaders and organizational representatives as they demonstrate new products, discuss exciting new services, and answer your questions.

Welcome Reception in the Exhibit Hall

Get the first look at the latest technologies and services! The Welcome Reception will be held in the Exhibit Hall on Thursday night with open bar and food. Mingle with exhibitors, attendees, and industry professionals...it's the perfect way to unwind from your travels and kick off ASNC2017!

Please note that children under the age of 18 (including children in strollers and carriers) are not allowed in the Exhibit Hall. This policy is in effect at all times in the Exhibit Hall including set-up and tear-down.

Lunch in the Exhibit Hall

Attendees receive two lunch coupons redeemable on Friday and Saturday at the ASNC Café located in the Exhibit Hall. Offering sandwiches, snacks, and beverages, the Café will be open 11:30 a.m.– 1:30 p.m.

Exhibitor Listing

Absolute Imaging Solutions 417
Absolute Imaging Solutions (AIS) is the Molecular Imaging experts in New/Reconditioned SPECT Cameras- Service- Processing Workstations and Parts. AIS is the exclusive source for the Mediso AnyScan® S, enabling healthcare providers a cost-effective NEW SPECT alternative with integration into various clinical settings.

American College of Radiology 423
The American College of Radiology is a leading professional medical society dedicated to serving patients and society by empowering radiology professionals to advance the practice, science, and professions of radiological care. ACR Accreditation and Appropriateness Criteria are the standards for safe imaging and patient care. The ACR's 37,000 members include radiologists, radiation oncologists, nuclear medicine physicians and medical physicists.

American Society of Nuclear Cardiology ..... Expo Hall Foyer
ASNC is the recognized leader in quality, education, advocacy and standards in cardiovascular imaging, with more than 4,000 members worldwide. ASNC is dedicated to continuous quality improvement, education, patient-centered imaging, and improving patient outcomes. ASNC establishes standards for excellence in cardiovascular imaging through the development of clinical guidelines, professional education, advocacy and research development for the cardiovascular community.

APCA 422
The Certification Board of Nuclear Cardiology (CBNC) and the Certification Board of Cardiovascular Computed Tomography (CBCCT) assessments are now a part of the Alliance for Physician Certification and Advancement™ (APCA™). APCA has over 21,000 certified physicians throughout the world and is part of the non-profit Inteleos™ family of certification alliances. The Certification Board of Nuclear Cardiology (CBNC) and the Certification Board of Cardiovascular Computed Tomography (CBCCT) certification programs were established to develop and administer practice-related examinations in the field of Nuclear Cardiology and Cardiovascular Computed Tomography and to award certification to those physicians who successfully complete the examination process.

Associated Imaging Services 425
Associated Imaging Services has been providing nuclear medicine service and sales throughout the Midwest since 1990. AIS can provide service on most all makes and models of gamma cameras. We also have solutions for departments who want to add or upgrade equipment, we have both new and refurbished options.

Astellas Pharma US, Inc. 312
Astellas Pharma US, Inc., is a U.S. affiliate of Tokyo-based Astellas Pharma Inc. Located in Northbrook, Illinois, the company serves as the headquarters for the Americas and employs nearly 3,000 people. Astellas is a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products.

BC Technical 508
BC Technical is the largest non-OEM provider of Medical Imaging Solutions. Our customers trust us to provide the best refurbished NM, SPECT/CT, PET, PET/CT, MRI and CT systems from all major OEMs.

Bracco Diagnostics Inc. 300
Bracco Diagnostics Inc. offers a product and solution portfolio for all key diagnostic imaging modalities: X-ray Imaging (including Computed Tomography-CT, Interventional Radiology, and Cardiac Catheterization), Magnetic Resonance Imaging (MRI), Contrast Enhanced Ultrasound (CEUS), and Nuclear Medicine through radioactive tracers. The diagnostic imaging portfolio is completed by a range of medical devices and advanced administration systems for contrast imaging products.

CardioNavix 403
CardioNavix provides the isotopes you need, for the equipment you already have. We remove the need for a fixed Rubidium-82 generator while maximizing your PET/CT investment.

Cardiovascular Imaging Technologies 327
CVIT is a research and development company focusing on practical solutions for achieving high-quality, maximally-efficient cardiac SPECT, PET, and CT imaging. CVIT offers training, preceptorships, processing software, and quality control software designed to improve quality and workflows in cardiac imaging. CVIT organizes, participates in, and functions as a core imaging lab for research studies leading to advances in the prevention, diagnosis, and treatment of cardiovascular diseases.

We have developed, 510(k) cleared, distributes and services the Imagen family of cardiac imaging products: ImagenPRO, ImagenMD, ImagenQ, Imagen3D, and our newest product ImagenSPECT. For more information, please contact Staci Courter at scourter@cvit.com or 816-531-2842 x 107."

Cedars-Sinai Medical Center 220
The Artificial Intelligence in Medicine (AIM) Program at Cedars-Sinai Medical Center develops software to process and analyze three-dimensional images of the heart as an experienced human operator would. The software and algorithms developed by the AIM Program at Cedars-Sinai are widely considered the gold standard in nuclear cardiology. Visit our booth to learn more about Cedars-Sinai Cardiac Suite and some of its latest features. We set the gold standard in customer service and patient satisfaction with diagnostic solutions that optimize imaging at the point of care. For healthcare facilities of all sizes, our SPECT and PET MPI services, nuclear products, and support offer outstanding flexibility to improve performance, optimize outcomes, and enhance the patient experience.

Digirad 212
Digirad sets the gold standard in customer service and patient satisfaction with diagnostic solutions that optimize imaging at the point of care. For healthcare facilities of all sizes, our SPECT and PET MPI services, nuclear products, and support offer outstanding flexibility to improve performance, optimize outcomes, and enhance the patient experience.

GE Healthcare.....409

GE Healthcare provides transformational medical technologies and services to meet the demand for increased access, enhanced quality and more affordable healthcare around the world. GE (NYSE: GE) works on things that matter - great people and technologies taking on tough challenges.

From medical imaging, software & IT, patient monitoring and diagnostics to drug discovery, biopharmaceutical manufacturing technologies and performance improvement solutions, GE Healthcare helps medical professionals deliver great healthcare to their patients.

Intersocietal Accreditation Commission.....321

For more than 25 years the IAC has followed its mission of Improving Health Care Through Accreditation, offering accreditation for vascular testing, echocardiography, nuclear/PET, MRI, CT, dental CT, carotid stenting, vein treatment and management, cardiac electrophysiology and cardiovascular catheterization. Learn about IAC's newest tools for your facility's quality goals including the QI Self-Assessment Tool, QI MOC Activity and QuickFill Reaccreditation by visiting us in the exhibit or at intersocietal.org.

ImageGuide Registry 325

The ImageGuide Registry is the first cardiovascular registry of its kind that provides the framework to support practices committed to continuous patient-centered imaging, practice transformation, and innovation. ImageGuide provides the tools to benchmark performance on location, practice, and national levels to achieve quality improvement. CMS has recognized ImageGuide as a Qualified Clinical Data Registry (QCDR) in 2017 for the third year in a row and can be used to meet reporting requirements under the Merit-based Incentive Payment System (MIPS).

INVIA.....223

INVIA is dedicated to developing advanced non-invasive cardiac imaging software for medical professionals to optimize patient care. Originating at the University of Michigan, 4DM provides physicians with an all-in-one solution for nuclear cardiac quantification, review, and reporting.

4DM is available integrated on the platforms of over 30 resellers, who range from large camera manufacturers, to review workstation providers and integrated PACS developers. Our resellers and INVIA also offer a stand-alone software-only solution – 4DM Personal.

Ionetix 415

Ionetix Corporation is the first national supplier of N-13 ammonia for use with cardiac Positron Emission Tomography (PET) imaging. N-13 Ammonia is a highly accurate myocardial perfusion imaging agent used for the detection of coronary artery disease (CAD) and is considered a gold standard for quantification of absolute coronary flow reserve (CFR). Ionetix has developed an ultra-compact, automated, unit dose N-13 ammonia production system. Ionetix will install this system directly at the hospital or clinic for on-demand dose availability, offering unprecedented access to N-13 Ammonia tracer supply.

Japanese Society of Nuclear Cardiology 518

The Japanese Society of Nuclear Cardiology (JSNC) is the leading society for nuclear cardiology in Japan.

The Japanese Society of Nuclear Cardiology (JSNC) is the leading society for nuclear cardiology in Japan, founded in October 1998. JSNC includes among its members cardiologists, nuclear medicine physicians, radiologists, technologists and other professionals dedicated to nuclear cardiology.

JSNC aims to promote basic and clinical research on nuclear cardiology and to contribute to international cooperation and the development of academic culture through research, education and clinical practice in nuclear cardiology. Every summer we hold annual scientific meeting. Since 2015, we have published our official English-language journal, Annals of Nuclear Cardiology (http://anc.jsnc.journal.org/), to promote clinical and research work in nuclear cardiology.

Jubilant DraxImage, Inc. 400

At Jubilant DraxImage, we are passionately dedicated to the field of Nuclear Medicine. Our leadership is driven by quality, safety and sustainability. Our mission is to discover, develop, manufacture and market innovative diagnostic and therapeutic radiopharmaceuticals and other technologies used in our field of

expertise. Through our ongoing support of the Nuclear Medicine community, we strive to accelerate, simplify and guide patient management.

Lantheus Medical Imaging, Inc. 108

Lantheus Medical Imaging (www.lantheus.com), a global leader in the development, manufacture and commercialization of innovative diagnostic imaging agents and products, is headquartered in North Billerica, Massachusetts with offices in Puerto Rico and Canada.

McGraw-Hill Education 113

With a strong editorial team, respected authors, and commitment to quality publications in all media, McGraw-Hill Education is a leading publisher of print and digital content in Cardiology. Visit our booth to browse our products including the landmark texts Nuclear Cardiology: Practical Applications, Hurst's the Heart and Harrison's Principles of Internal Medicine. Web: www.mcgrawhillmedical.com

MiE America 420

MiE America leads the way in re-manufacturing and manufacturer of the nuclear medicine imaging. Our SPECT and PET scanners are FDA and CE approved and controlled by SCINTRON. This new computer system provides the most current acquisition and processing protocols to allow Nuclear Medicine, Cardiology providers or Researchers to deliver high quality diagnostic scans to their patients, but also purchase and/or upgrade to today's technology economically: 3D imaging, dose reduction, faster and state of the art processing, longevity, more efficient use of your RB-82 generator and cost reduction. Please stop by at our booth for a demonstration or visit our webpage www.mieamerica.com for more information.

MIM Software Inc. 323

MIM Software Inc. provides vendor-neutral solutions for multi-modality image fusion, processing, and review for radiology and nuclear medicine. MIMcardiac® is a vendor-neutral solution for the quantitative analysis of cardiac PET and SPECT. LV parameters are generated using a robust and accurate deformable registration method helping to overcome limitations of traditional threshold methods. Fusion between stress/rest images facilitates comparison of corresponding myocardium and perfusion differences are highlighted in a color-coded display.

Exhibitor Listing (cont.)

Multi-modality fusion is also used to register functional images to CCTA and to correct PET/CT and SPECT/CT misalignment.

Molecular Imaging Services, Inc. 317

Molecular Imaging Services, Inc. (MIS) is a privately held company with headquarters in Newark, Delaware. We Specialize in Cardiac PET and SPECT In-Office Cardiology Imaging Solutions. Our Comprehensive Support approach has redefined the turnkey model with unparalleled Clinical, Operational and Reimbursement resources and solutions. If you are looking to add Cardiac PET to your practice stop by and meet the MIS Team at Booth # 317.

Nuclear Imaging Services, LLC 319

Nuclear Imaging Services, LLC is a leading provider of nuclear cardiology turnkey solutions. We provide refurbished equipment, parts, and nationwide service and clinical support for SPECT, PET, and PET/CT imaging.

Nuclear Medicine Technology Certification Board 516

The NMTCB is the Nuclear Medicine Technology Certification Board, formed for the purpose of creating and maintaining examinations for nuclear medicine technologists (NMTs). Since 1978, the NMTCB has offered high-quality certification exams for NMTs to become Certified Nuclear Medicine Technologists (CNMT). The NMTCB provides five certification programs: the entry level CNMT credential, the post-primary NMTCB(CT) credential for computed tomography, the PET specialty credential for positron emission tomography certification, the NCT specialty credential for nuclear cardiology, and the NMAA credential for NMT's who have graduated from a recognized Master's level program as a Nuclear Medicine Advanced Associate. NMTCB is also developing a sixth certification program, the NMTCB(RS), which will be a radiation safety credential specifically for nuclear medicine technologists.

Philips 412

Philips is a health technology company focused on improving people's lives through meaningful innovation across the health continuum – from healthy living and prevention to diagnosis, treatment and home care. Applying advanced technologies and deep clinical and consumer insights, Philips partners with customers to deliver integrated solutions that enable better outcomes at lower cost.

PMOD Technologies Inc. 512

PMOD Technologies aims to equip researchers with best-in-class software tools for biomedical imag-ing in humans and animals. The PMOD tool suite arguably represents the leading solution for PET ki-netic modeling. PMOD's PCARD tool offers a comprehensive environment for the analysis of cardiac PET images, supporting static, dynamic and gated studies. Moreover, qualitative and quantitative CMR image analysis is being supported. PMOD's expanding customer base comprises more than 500 sites worldwide. "Secure. Flexible. Accessible. ScImage's PICOM365 Enterprise PACS delivers secure on-demand access to all patient images when and where you need them.

ScImage 514

Whether you're an independent practice with no internal IT support or a multi-hospital system with specific security requirements, PICOM365 offers options for on-premise, cloud and hybrid implementations across all imaging departments. Utilizing your existing cameras, ScImage's PICOM365 Enterprise PACS offers tight integration with two leading nuclear cardiology quantification software solutions. Image sharing, structured reporting and comprehensive analytics optimize your departmental workflows. Learn more at www.scimage.com."

Siemens Healthineers 313

Siemens Healthineers is committed to becoming the trusted partner of healthcare providers worldwide, enabling them to improve patient outcomes while reducing costs. Driven by our long legacy of engineering excellence and our pioneering approach to developing the latest advancements, we are a global leader in medical imaging, laboratory diagnostics, clinical IT, and services. Siemens Healthineers is dedicated to helping our partners be successful – clinically, operationally and financially – from prevention through diagnosis and treatment. To learn more about Siemens Healthineers, please visit usa.siemens.com/Healthineers.

Southwestern Imaging Systems and Service 421

We started Southwestern Imaging Systems & Service (SWISS) in 2002 with the singular goal of being a reliable and trustworthy provider of sales and services to the medical imaging field. Through the years, we have built a team of experienced imaging equipment engineers, technicians and support personnel that is committed to meeting the changing demands of our customers. We strive to offer affordable diagnostic equipment and support services to meet those demands.

Our goal is to ensure customers are treated equitably. We charge competitive rates for our services and never push services, packages or equipment that are not the right fit for your organization or operation. We have built SWISS for the long term, with customer relationships developed based on responsiveness, integrity and mutual respect.

We service a wide range of imaging equipment on a contract basis, ensuring system availability and long-term reliability. We also supply the parts needed by our customers and offer a selection of refurbished imaging equipment for purchase. For service, parts and imaging equipment sales, we focus on the following: MRI, PET-CT, Cardiac PET, Nuclear Medicine, Nuclear Cardiology.At SWISS, we understand the "one size fits all" approach other OEMs and providers take is often not consistent with the unique, individualized needs of our customers. Instead of forcing our customers to work "our way," we provide products and services in a way that work for you.

Spectrum Dynamics Medical 200

Spectrum Dynamics Medical revolutionized the practice of nuclear cardiology with the 1st clinical & commercially available CZT imaging scanner.

The D-SPECT® and D-SPECT-L™ nuclear cardiology imaging systems dramatically enhances image quality, improves workflow, allows the ability to reduce radiation exposure by implementing unique low dose protocols and provides the platform for advanced imaging protocols, i.e. Dynamic SPECT and Simultaneous Multi Isotope.

For more information, visit www.spectrum-dynamics.com or call 1-941-256-3660. Please visit us at Booth 200.

Syntermed, Inc. 414

Syntermed, Inc., an Atlanta-based imaging and informatics software company, is a global leader in providing cardiac and neuro solutions for SPECT and PET. Its solutions power over 50% of the nuclear medicine departments worldwide. Signature products include Emory Toolbox™, Syntermed Live™, Syntermed IDS™, SmartReport™, Synctools™, Adreview™ Tools, PETtools™, Flowtool™ and NeuroQ™. Syntermed software is compatible with virtually any nuclear medicine workstation or PC/MAC that supports Microsoft® Windows® operating systems and is available direct or from leading OEMs, PACs vendors, and Systems Integrators. Please join us in booth 414 to learn more about how to use MPI LV Dyssynchrony tools to guide CRT, plus QC tools specific for measuring blood flow. For more information email info@syntermed.com, visit www.syntermedcom, or call 888.263.4446.

Triad Isotopes 401

AT TRIAD ISOTOPES, NUCLEAR PHARMACY ISN'T JUST OUR CORE BUSINESS, IT'S OUR ONLY BUSINESS. Triad Isotopes is proud of our reputation for outstanding service, which has helped us become the second-largest and fastest-growing radiopharmaceutical specialist in the country. We are proud of the relationships we have with thousands of hospitals, physicians and nuclear medicine providers nationwide that consider us partners in delivering their patients the custom solutions they rely on for diagnosis and treatment. With nearly 30 years of experience in preparing radioisotopes, Triad Isotopes delivers customized solutions and industry expertise that consistently exceed our customers' expectations. We also offer choice. Our open formulary allows clinicians to select their preferred agents to achieve the highest patient benefiit. Today, our 54 locations nationwide serve over 4 million patients annually. To discover more, visit us at www.triadisotopes.com"

Wolters Kluwer 424

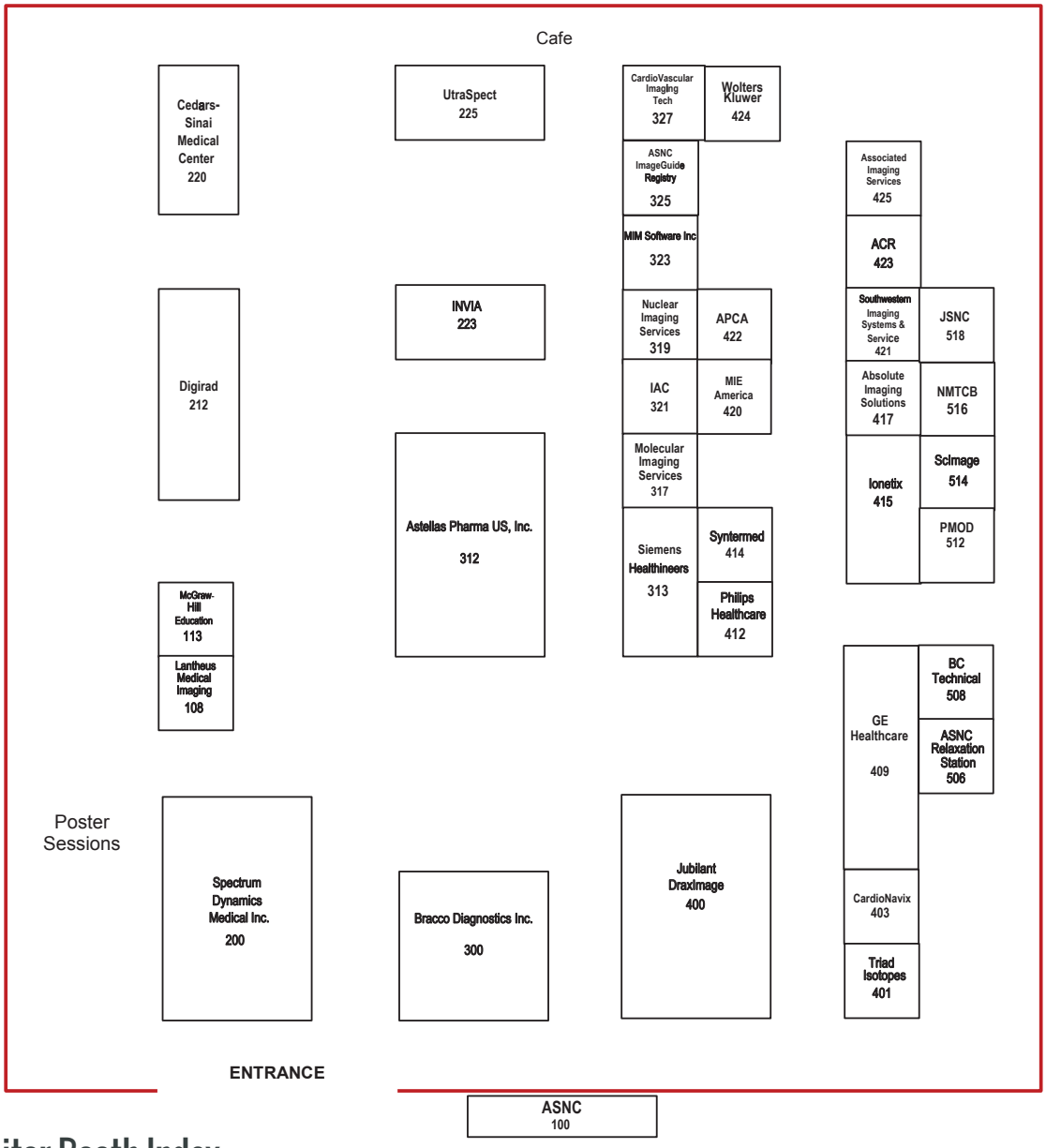
Wolters Kluwer Health company is a leading international publisher of medical books, journals, and electronic media. We proudly offer specialized publications and software for physicians, nurses, students and clinicians. Please visit our booth to browse our comprehensive product line.

UltraSPECT, Inc. 225

UltraSPECT Inc. is a leading provider of image reconstruction solutions that support safer and faster imaging in nuclear cardiac and oncology exams, with better diagnostic capabilities. At a fraction of the cost of a brand new camera, Xpress.Cardiac™, Xpress3.Cardiac™ and Xpress/Xact.Bone™ provide value to physicians, technologists, patients, administrators and radiopharmaceutical suppliers.

The proprietary, innovative Wide-Beam Reconstruction (WBR™) image processing algorithm addresses the clinical need for significant reduction in injection dose and shortened scan times, boosting patient safety, throughput and comfort. Healthcare facilities of all sizes maximize value from the ability to leverage the investment in existing nuclear medicine cameras and processing stations– regardless of the manufacturer, model and age. Moreover, UltraSPECT solutions enable healthcare facilities to meet the American Society of Nuclear Cardiology (ASNC) low-dose guidelines. UltraSPECT image reconstruction products are approved by the FDA, as well as numerous regulatory authorities in Europe and Asia. For more information, visit www.ultraspect.com or call 1-888-WBR-SCAN (1-888-927-7226).

Exhibitor Floorplan



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ASNC 2018

23rd Annual Scientific Session
American Society of Nuclear Cardiology

September 6-9, 2018
San Francisco, California
San Francisco Marriott Marquis

Save the Date
September 6-9!

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ASNC Institute for the Advancement of Nuclear Cardiology

The ASNC Fund

Shaping the Future of Nuclear Cardiac Imaging

Pledge your gift to The ASNC Fund and support the Institute for the Advancement of Nuclear Cardiology (IANC) today!

The mission of the IANC is to advance the field of nuclear cardiology through the support of research and innovation, promoting the continued development of the essential disciplines, and patient education.

The IANC will award the first research grant of $50,000 in 2018. Please do your part to support innovative, patient-centric research and education in the field of nuclear cardiology.

All gifts make a difference! Pledge forms are available at the ASNC Booth located in the Expo Foyer.

Gifts are 100% tax deductible.

Industry Sponsored Satellite Symposia

These activities are not part of the official ASNC2017 Annual Scientific Session as planned by the Program Committee.

Friday, September 15, 2017

Lunch and Learn

12:15 – 1:15 p.m. | New York

D-SPECT + CFR = NOW

FACULTY:

Josh Gurewitz, VP, Sales & Marketing Spectrum Dynamics Medical

Professor Denis Agostini, M.D., PhD, Head of Nuclear Medicine Department Université Hôpital Caen-Normandie Caen, France

Dr. Alejandro H. Meretta, Chief of Nuclear Cardiology, Instituto Cardiovascular de Buenos Aires Buenos Aires, Argentina

Presented by Spectrum Dynamics

Lunch and Learn

12:15 – 1:15 p.m. | Atlanta

Introducing the Philips CardioMD IV

FACULTY:

Raffi Kayayan, PhD, Senior Manager, Product Marketing Advanced Molecular Imaging, Philips

Presented by Philips

Evening Satellite

6:30 – 7:45pm | New York

Imaging Flow Using Cardiac Pet: How And Why

FACULTY:

Hein J. Verberne, MD, PhD Associate Professor, Academic Medical Center, University of Amsterdam

PET-guided Interventional Physiology

FACULTY:

Nils P. Johnson, MD, MS, Associate Professor, Cardiovascular Medicine at UT Health, The University of Texas Health Science Center at Houston, McGovern Medical School

Presented by Ionetix

Saturday, September 16, 2017

Breakfast Satellite

6:30 – 7:55am | Chicago AB

Adding New Clinical Value to Nuclear Cardiology Procedures

FACULTY:

David Cooke, MSEE, Emory University

Kenneth Nichols, PhD, Long Island Jewish Health System

Ernest Garcia, PhD, Emory University

Presented by Syntermed

Lunch and Learn

12:15 – 1:15 p.m. | Atlanta

PET Gatekeeper Guided Revascularization of Severely Reduced Coronary Flow Capacity Significantly Lowers MI and Death But Not For Mild to Moderate Perfusion Abnormalities

FACULTY:

K. Lance Gould, MD, SNM, Professor of Cardiovascular Medicine and Executive Director, Weatherhead P.E.T. Center For Preventing and Reversing Atherosclerosis, McGovern Medical School, University of Texas - Houston

Presented by Bracco

Lunch and Learn

12:15 – 1:15 p.m. | New York

Advances in Nuclear Cardiology: From Injection to Imaging

FACULTY:

Manuel D. Cerqueira, MD, MASNC Cleveland Clinic Lerner College of Medicine, Cleveland Clinic

Terrence D. Ruddy, MD, FASNC University of Ottawa Heart Institute

Marcelo F. Di Carli, MD Brigham and Women's Hospital

Presented by GE Healthcare

Cardiogen-82®

(Rubidium Rb 82 Generator)

for Positron Emission Tomography Myocardial Perfusion Imaging

Nuclear Medicine Suite

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In 1989, **Bracco was the first** to invest heavily in cardiac PET MPI, and the legacy of excellence and service continues today.

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The individuals shown are for illustrative purposes only. All persons depicted are models and not real patients/physicians.

CardioGen-82 (Rubidium Rb 82 Generator) is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

IMPORTANT SAFETY INFORMATION:

WARNING: UNINTENDED STRONTIUM-82 (Sr-82) AND STRONTIUM-85 (Sr-85) RADIATION EXPOSURE

Unintended radiation exposure occurs when the levels of Sr-82 or Sr-85 in the rubidium Rb 82 chloride injection exceed specified limits *[see Warnings and Precautions (5.1)]*.

Perform generator eluate tests:

1) Record each generator eluate volume, including waste and test volumes, and keep a record of the cumulative eluate volume *[see Dosage and Administration (2.4)]*.
2) Determine Rb-82, Sr-82, Sr-85 levels in the eluate:
   - Once daily, prior to any drug administrations, and
   - At additional daily tests after detection of an Alert Limit. Alert Limits are:
     - 14 L for the generator's cumulative eluate volume, or
     - An eluate Sr-82 level of 0.002 µCi/mCi Rb-82, or
     - An eluate Sr-85 level of 0.02 µCi/mCi Rb-82.
     - Perform the additional daily tests at time points determined by the day's elution volume; tests are performed every 750 mL *[see Dosage and Administration (2.5)]*.
3) Stop use of a generator at an Expiration Limit of:
     - 17 L for the generator's cumulative eluate volume, or
     - 42 days post generator calibration date, or
     - An eluate Sr-82 level of 0.01 µCi/mCi Rb-82, or
     - An eluate Sr-85 level of 0.1 µCi/mCi Rb-82 *[see Dosage and Administration (2.6)]*.

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform pharmacologic stress testing in accordance with the pharmacologic stress agent's prescribing information and only in the setting where cardiac resuscitation equipment and trained staff are readily available.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/safety/medwatch, or call 1-800-FDA-1088.

Please consult brief summary of the full Prescribing Information for CardioGen-82 (Rubidium Rb 82 Generator) including boxed **WARNING** on previous page.

CardioGen-82 (Rubidium Rb 82 Generator) is manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831, by GE Healthcare, Medi-Physics, Inc., South Plainfield, NJ 07080

CardioGen-82 is a registered trademark of, and We are Cardiac PET is a trademark of, Bracco Diagnostics Inc.

Bracco Diagnostics Inc., 259 Prospect Plains Road, Building H, Monroe Township, NJ 08831 USA
Phone: 609-514-2200 | **Toll Free:** 1-877-272-2269 (U.S. only) | **Fax:** 609-514-2446

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Bracco Diagnostics

CARDIOGEN-82®
(Rubidium Rb 82 Generator)

Rx only
Please see full prescribing information.
A brief summary follows.

WARNING: UNINTENDED STRONTIUM-82 (Sr-82) AND STRONTIUM-85 (Sr-85) RADIATION EXPOSURE

Unintended radiation exposure occurs when the levels of Sr-82 or Sr-85 in the rubidium Rb 82 chloride injection exceed specified limits [*see Warnings and Precautions (5.1)*]

Perform generator eluate tests:

1) Record each generator eluate volume, including waste and test volumes, and keep a record of the cumulative eluate volume [*see Dosage and Administration (2.4)*].

2) Determine Rb-82, Sr-82, Sr-85 in the generator eluate:
- **Once a day, prior to any drug administrations, and**
- **At additional daily tests after detection of an Alert Limit. Alert Limits are:**
  - **o 14 L for the generator's cumulative eluate volume, or**
  - **o An eluate Sr-82 level of 0.002 µCi/ mCi Rb-82, or**
  - **o An eluate Sr-85 level of 0.02 Sr-85 µCi/ mCi Rb-82.**
  - **o Perform the additional daily tests at time points determined by the day's elution volume; tests are performed every 750 mL [*see Dosage and Administration (2.5)*].**

3) Stop use of a generator at an Expiration Limit of:
- **o 17 L for the generator's cumulative eluate volume, or**
- **o 42 days post generator calibration date, or**
- **o An eluate Sr-82 level of 0.01 µCi /mCi Rb-82, or**
- **o An eluate Sr-85 level of 0.1 µCi /mCi Rb-82 [*see Dosage and Administration (2.6)*].**

1 INDICATIONS AND USAGE CardioGen-82 is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

2 DOSAGE AND ADMINISTRATION

2.1 Infusion System Use CardioGen-82 only with an infusion system specifically designed for use with the generator and capable of accurate measurement and delivery of doses of rubidium Rb 82 chloride injection. Follow instructions in the Infusion System User's Guide for the set up and intravenous infusion of rubidium Rb 82 chloride injection dose(s).

2.2 Rubidium Rb 82 Chloride Injection Dosage The recommended adult single dose of rubidium Rb 82 chloride injection is 1480 MBq (40 mCi) with a range of 1110-2220 MBq (30-60 mCi).
- Do not exceed a single dose of 2220 MBq (60 mCi).
- Use the lowest dose necessary to obtain adequate cardiac visualization consistent with the dosing goal of as low as reasonably achievable (ALARA).
- Individualize the dose by considering factors such as body size, and the imaging equipment and technique.
- Administer the single dose at 50 mL/minute through a catheter inserted into a large peripheral vein; do not to exceed a total infusion volume of 100 mL.

Administer two separate single doses to complete rest and stress myocardial perfusion imaging as follows:

For rest imaging:
- Administer a single ("rest") rubidium Rb-82 chloride dose;
- Start imaging 60-90 seconds after completion of the infusion of the rest dose and acquire images for 5 minutes; if a longer circulation time is anticipated (e.g., in a patient with severe left ventricular dysfunction), start imaging 120 seconds after the rest dose.

For stress imaging:
- Begin the study 10 minutes after completion of the resting dose infusion, to allow for sufficient Rb-82 decay;
- Administer a pharmacologic stress agent in accordance with its prescribing information;
- After an interval of 3 minutes, infuse a single ("stress") rubidium Rb-82 chloride dose;
- Start imaging 60-90 seconds after completion of the stress Rb-82 chloride dose infusion and acquire images for 5 minutes; if a longer circulation time is anticipated start imaging 120 sec after the stress dose.

2.3 Drug Handling
- Limit the use of radiopharmaceuticals to physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Wear waterproof gloves and effective shielding when handling rubidium Rb-82 chloride injection and the infusion system.
- Observe aseptic techniques in all drug handling.
- Use only additive-free Sodium Chloride Injection USP to elute the generator.
- Visually inspect the drug for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer eluate from the generator if there is any evidence of foreign matter.

2.4 Directions for Eluting Rubidium Rb 82 Chloride Injection
- Allow at least 10 minutes between elutions for regeneration of Rb-82.
- Elute with additive-free Sodium Chloride Injection USP only. Additives (particularly calcium ions, to which strontium ions are chemically analogous), may cause the release of substantial amounts of Sr-82 and/or Sr-85 into the eluate regardless of the age or prior use of the generator.
- Discard the first 50 mL eluate each day the generator is first eluted. Employ proper safety precautions since the eluate contains radioactivity.
- Maintain an on-going record of all eluate volumes (washing, testing, dosing volumes), including a summary of the cumulative volume of eluate from the generator.

2.5 Eluate Testing Protocol

Use additive-free sodium chloride injection USP for all elutions. Apply aseptic technique throughout.

Before administering rubidium Rb 82 chloride injection to the first patient each day, perform the following test:

Strontium Alert Limits and Mandatory Eluate Testing:
- Use an ionization chamber-type dose calibrator for eluate testing.
- Daily, before administering rubidium Rb 82 chloride injection to any patient, perform an eluate testing to determine Rb-82, Sr-82, and Sr-85 levels
- Perform additional daily eluate tests after detecting any of the following Alert Limits:
  - o 14 L total elution volume has passed through the generator column, or
  - o Sr-82 level reaches 0.002 µCi per mCi Rb-82, or
  - o Sr-85 level reaches 0.02 µCi per mCi Rb-82.

Perform the additional daily eluate tests at time points determined by the day's elution volume; tests are performed every 750 mL.
- o For example, if an Alert Limit were reached and the clinical site eluted less than 750 mL from the generator during the day, then no additional eluate tests would have been performed that day.
- o If the same clinical site the next day eluted 1,500 mL from the generator, then the site would have performed three tests that day: 1) the required daily test that precedes any patient dosing, 2) a test at the 750 mL elution point, and 3) a test at the 1,500 mL elution point.
- o If a generator's Alert Limit is reached, the clinical site performs the additional daily tests (at intervals of 750 mL) each subsequent day the generator is used. The additional tests are necessary to promptly detect excessive Sr-82 and/or Sr-85 in eluates.

Rubidium Eluate Level Testing:

1. Set a dose calibrator for Rb-82 as recommended by the manufacturer or use the Co-60 setting and divide the reading obtained by 0.548. Obtain the reading from the instrument in millicuries.
2. Elute the generator with 50 mL of Sodium Chloride Injection USP and discard the eluate (first elution).
3. Allow at least 10 minutes for the regeneration of Rb-82, then elute the generator with 50 mL of Sodium Chloride Injection USP at a rate of 50 mL/min and collect the eluate in a stoppered glass vial (plastic containers are not suitable). Note the exact time of end of elution (E.O.E.).
4. Using the dose calibrator, determine the activity of Rb-82 and note the time of the reading. Correct the reading for decay to the E.O.E. using the appropriate decay factor for Rb-82 (see Table 1).

Note: If the reading is taken 2 1/2 minutes after end of elution, multiply the dose calibrator reading by 4 to correct for decay.

Strontium Eluate Level Testing:

5. Using the sample obtained for the Rb-82 activity determination, allow the sample to stand for at least one hour to allow for the complete decay of Rb-82.
6. Measure the activity of the sample in a dose calibrator at the setting recommended by the manufacturer for Rb-82 and/or Sr-82. As an alternative, use the Co-60 setting and the reading obtained divided by 0.548.

Set the instrument to read in microcuries and record the reading in the display.

7. Calculate the ratio (R) of Sr-85/Sr-82 on the day (postcalibration) of the measurement using the ratio of Sr- 85/Sr-82 on the day of calibration provided on the generator label and the Sr-85/Sr-82 Ratio Factor from Table 2. Determine R using the following equation:

$$R = \frac{[Sr\text{-}85]}{[Sr\text{-}82]}$$ on calibration date X Ratio Factor on the day (post-calibration) of measurement

8. Use a correction factor (F) of 0.478 to compensate for the contribution of Sr-85 to the reading.
9. Calculate the amount of Sr-82 in the sample using the following equation:

$$Sr\text{-}82\ (\mu Ci) = \frac{\text{dose calibration reading } (\mu Ci)}{[1 + (R)\ (F)]}$$

Example: dose calibrator reading (µCi) = 0.8; Sr85/Sr82 ratio (R) =1.48; correction factor (F) = 0.478.

$$Sr\text{-}82\ (\mu Ci) = \frac{0.8}{[1 + (1.48)(0.478)]} = 0.47$$

10. Determine if Sr-82 in the eluate exceeds an Alert or Expiration Limit by dividing the µCi of Sr-82 by the mCi of Rb-82 at End of Elution (see below for further instructions based on the Sr-82 level)

Example: 0.47 µCi of Sr-82; 50 mCi of Rb-82 E.O.E.

$$\frac{0.47\ \mu Ci\ Sr\text{-}82}{50\ mCi\ Rb\text{-}82} = 0.0094\ \mu Ci/mCi\ Rb\text{-}82$$ (is above Alert Limit of 0.002; additional daily eluate testing must be performed)

11. Determine if Sr-85 in the eluate exceeds an Alert or Expiration Limit by multiplying the result obtained in step 10 by (R) as calculated in step 7 (above).

Example: 0.0094 x 1.48 = 0.014 µCi Sr-85/mCi Rb-82 (test result is below Alert and Expiration Limits)

Use Table 1 to calculate the decay factor for Rb-82; step 4 (above).

TABLE 1
Physical Decay Chart: Rb-82 half-life 75 seconds

Seconds	Fraction Remaining	Seconds	Fraction Remaining
0*	1.000	165	0.218
15	0.871	180	0.190
30	0.758	195	0.165
45	0.660	210	0.144
60	0.574	225	0.125
75	0.500	240	0.109
90	0.435	255	0.095
105	0.379	270	0.083
120	0.330	285	0.072
135	0.287	300	0.063
150	0.250		

*Elution time

Use Table 2 to calculate the ratio (R) of Sr-85/Sr-82; step 7 (above).

TABLE 2
Sr-85/Sr-82 Ratio Chart (Sr-85 T ½ = 65 days, Sr-82 ½ = 25 days)

Days	Ratio Factor	Days	Ratio Factor	Days	Ratio Factor
0*	1.00	16	1.31	32	1.73
1	1.02	17	1.34	33	1.76
2	1.03	18	1.36	34	1.79
3	1.05	19	1.38	35	1.82
4	1.07	20	1.41	36	1.85
5	1.09	21	1.43	37	1.88
6	1.11	22	1.46	38	1.91
7	1.13	23	1.48	39	1.95
8	1.15	24	1.51	40	1.98
9	1.17	25	1.53	41	2.01
10	1.19	26	1.56	42	2.05
11	1.21	27	1.58		
12	1.23	28	1.61		
13	1.25	29	1.64		
14	1.27	30	1.67		
15	1.29	31	1.70		

*Day of calibration

2.6 CardioGen-82 Expiration Stop use of the CardioGen-82 generator once any one of the following Expiration Limits is reached.
- A total elution volume of 17 L has passed through the generator column, or
- 42 days post calibration date, or
- An eluate Sr-82 level of 0.01 µCi /mCi Rb-82, or
- An eluate Sr-85 level of 0.1 µCi /mCi Rb-82.

2.7 Radiation Dosimetry The estimated absorbed radiation doses for Rb-82, Sr-82, and Sr-85 from an intravenous injection rubidium Rb- 82 chloride are shown in Table 3.

3 DOSAGE FORMS AND STRENGTHS CardioGen-82 is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. CardioGen-82 consists of strontium Sr-82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time.

4 CONTRAINDICATIONS None.

5 WARNINGS AND PRECAUTIONS

5.1 Unintended Sr-82 and Sr-85 Exposure Unintended radiation exposure occurs when the Sr-82 and Sr-85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits. Unintended exposure to strontium radiation has occurred in some patients who received rubidium Rb 82 injections at clinical sites where generator eluate testing appeared insufficient. The physical half lives of Sr-82 and Sr-85 are 25 days and 65 days, respectively, in contrast to Rb-82 which has a physical half-life of 75 seconds. Unintended exposure to strontium radiation contributes to a patient's overall cumulative radiation dose [*see Warnings and Precautions (5.4)*].

To minimize the risk of unintended radiation exposure, strict adherence to a daily eluate testing protocol is required. Stop using the rubidium generator when the expiration limits are reached [*see Dosage and Administration (2.5) and (2.6)*].

5.2 Risks Associated with Pharmacologic Stress Pharmacologic induction of cardiovascular stress may be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform pharmacologic stress testing in accordance with the pharmacologic stress agent's prescribing information and only in the setting where cardiac resuscitation equipment and trained staff are readily available.

5.3 Volume Overload Patients with congestive heart failure or the elderly may experience a transitory increase in circulatory volume load. Observe these patients during infusion and for several hours following rubidium chloride injection administration to detect delayed hemodynamic disturbances.

5.4 Cumulative Radiation Exposure: Long-Term Risk of Cancer Rubidium Rb 82 chloride injection, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Use the lowest dose of rubidium Rb 82 chloride injection necessary for imaging and ensure safe handling to protect the patient and health care worker [*see Dosage and Administration (2.2) and (2.3)*]. Encourage patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.

TABLE 3
Adult Absorbed Radiation Dose Coefficient

Organ[a,b]	Rb-82 (Average for Rest and Stress) mrem/mCi (µSv/3.7 MBq)[c]	Sr-82 mrem/µCi (µSv/3.7kBq)[c]	Sr-85 mrem/µCi (µSv/3.7kBq)[c]
Adrenals	7.56	10.6	5.03
Bone --			
Osteogenic cells	1.86	----	---
Bone Surface	---	107	9.81
Brain	0.60	8.29	2.96
Breast	0.82	7.03	1.72
Gall Bladder Wall	3.17	8.47	2.82
Heart Wall	16.5	8.18	2.67
Kidneys	20.04	9.18	2.50
Liver	4.20	8.10	2.50
Lower Large Intestine Wall	2.84	51.8	5.14
Lungs[d]	10.7	8.25	2.84
Muscles	1.29	8.14	2.66
Ovaries	1.41	10.2	4.29
Pancreas	8.85	9.10	3.46
Red Marrow	1.19	91.0	9.84
Skin	1.14	7.03	1.75
Small Intestine	4.76	9.62	4.03
Spleen	6.61	8.10	2.54
Stomach	8.14	7.84	2.26
Testes	0.82	7.25	1.70
Thymus	1.49	7.84	2.33
Thyroid	6.11	8.07	2.57
Upper Large Intestine	5.94	23.7	3.62
Urinary Bladder Wall	1.61	21.9	2.90
Uterus	3.72	9.14	3.32
Total Body	1.77	Not Calculated	Not Calculated
Effective Dose[e]	4.74[f]	23.4	4.03

[a]Rb-82 doses are averages of rest and stress dosimetry data (see Senthamizhchelvan et al. 1,2). To calculate organ doses (mrem) from Rb-82, multiply the dose coefficient for each organ by the administered activity in mCi.

[b]Sr-82 and Sr-85 doses are calculated using software package DCAL and ICRP dose coefficients. To calculate organ doses (mrem) attributable to Sr-82, and Sr-85, multiply the dose coefficients by the calculated amounts of strontium in µCi.3

[c] To convert to SI units, insert the dose coefficient into the formula in parentheses, e.g. for adrenals 7.56 mrem/mCi = 7.56 µSv/37 MBq = 2.04 x 10-13 Sv/Bq .

[d] Calculated from ICRP 66

[e] Calculated from ICRP 60

[f] Stress phase only

6 ADVERSE REACTIONS

6.1 Postmarketing Experience The following serious adverse reactions have been identified during postapproval use of CardioGen-82. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Unintended radiation exposure has occurred in some patients who received rubidium Rb 82 chloride injections at clinical sites where generator eluate testing appeared insufficient [*see Boxed Warning, Warnings and Precautions (5.1), and Dosage and Administration (2.5)*].

7 DRUG INTERACTIONS Specific drug-drug interactions have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C Animal reproductive studies have not been conducted with rubidium Rb 82 chloride injection. It is also not known whether rubidium Rb 82 chloride injection can cause fetal harm when administered to a pregnant woman; however, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering rubidium Rb 82 chloride injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from rubidium Rb-82 and the gestational timing of exposure. Administer rubidium Rb-82 to a pregnant woman only if clearly needed.

8.3 Nursing Mothers It is not known whether rubidium Rb 82 chloride injection is excreted in human milk. Due to the short halflife of rubidium Rb-82 (75 seconds) it is unlikely that the drug would be excreted in human milk during lactation. However, because many drugs are excreted in human milk, caution should be exercised when rubidium Rb-82 chloride injection is administered to nursing women. Do not resume breastfeeding until one hour after the last infusion.

8.4 Pediatric Use Rubidium Rb 82 chloride injection safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use In elderly patients with a clinically important decrease in cardiac function, lengthen the delay between infusion and image acquisition [*see Dosage and Administration (2.2)*]. Observe for the possibility of fluid overload [*see Warnings and Precautions (5.3)*].

8.6 Renal Impairment Reductions in renal function are not anticipated to alter clearance of rubidium Rb 82 chloride injection because Rb-82 decays to stable Kr-82 with a half-life of 75 seconds and Kr-82 is exhaled through the lungs.

8.7 Hepatic Impairment Reductions in hepatic function are not anticipated to alter clearance of rubidium Rb 82 chloride injection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 chloride injection may affect fertility in males or females.

14 CLINICAL STUDIES In a descriptive, prospective, blinded image interpretation study6 of adult patients with known or suspected coronary artery disease, myocardial perfusion deficits in stress and rest PET images obtained with ammonia N 13 (n = 111) or rubidium Rb-82 chloride (n = 82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a scale of 0 (normal) to 5 (severe). Values for stenosis flow reserve, defined as flow at maximum coronary vasodilatation relative to rest flow, ranged from 0 (total occlusion) to 5 (normal). With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

A systematic review of published literature was conducted using pre-defined inclusion/exclusion criteria which resulted in identification of 10 studies evaluating the use of Rb-82 PET myocardial perfusion imaging (MPI) for the identification of coronary artery disease as defined by catheter-based angiography.

In these studies, the patient was the unit of analysis and 50% stenosis was the threshold for clinically significant coronary artery disease (CAD). Of these 10 studies, 9 studies were included in a meta-analysis for sensitivity (excluding one study with 100% sensitivity) and 7 studies were included in a meta-analysis of specificity (excluding 3 studies with 100% specificity). A random effects model yielded overall estimates of sensitivity and specificity of 92% (95% CI: 89% to 95%) and 81% (95% CI: 76% to 86%), respectively. The use of meta-analysis in establishing performance characteristics is limited, particularly by the possibility of publication bias (positive results being more likely to be published than negative results) which is difficult to detect especially when based on a limited number of small studies.

17 PATIENT COUNSELING INFORMATION

17.1 Women of Childbearing Potential Patients should be advised to inform their physician or healthcare provider if they are pregnant or breastfeeding.

17.2 Post-study Breastfeeding Avoidance Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for one hour afteradministration of rubidium Rb 82 chloride injection.

17.3 Post-study Voiding Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after completion of the PET scan.

Manufactured for
Bracco Diagnostics Inc., Monroe Twp., NJ 08831 by Medi-Physics, Inc., South Plainfield, NJ 07080
US Patent 7,504,646 Revised May 2014

MEET AUGIE

Everyone who knows Augie also knows that he's a hopeless romantic. He's the guy who asked his wife to marry him twice. The guy who does everything with love—whether it's washing his truck in the driveway on a sunny day or taking out the trash. The guy who has a romantic affinity for spicy food. What everyone doesn't know—including Augie—is that his heartburn after those ultra-spicy tacos isn't really heartburn. It's chest pain.

Step into Augie's world at Astellas Booth 312 at ASNC2017. There, you'll find resources that can help benefit patients with big hearts like Augie.

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EXHIBIT 15

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

In the Matter of	
CERTAIN STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS AND COMPONENTS THEREOF INCLUDING GENERATORS	Investigation No. 337-TA-____

FOREIGN COUNTERPARTS TO THE ASSERTED PATENTS

The following tables contain information on foreign counterparts of the Asserted Patents with an indication of each reference's prosecution status.

Foreign Country	Foreign Application Number	Foreign Counterpart	Prosecution Status
AU		2009257432	Granted
AU		2015200752	Granted
AU	2017235989		Pending
BR	PI0913271-6		Pending
CA		2,724,645	Granted
CA	TBA		Pending
CN		ZL200980121946.0	Granted
CN	201510165747.7		Published
EP	9763612		Published
IN	8788/DELNP/2010		Pending
KR		10-1618855	Granted
KR		10-1717904	Granted
KR		10-1812075	Granted
KR	1020177036474		Pending
RU		2512939	Granted
RU	2014105196		Published
SG		166470	Granted
SG		192404	Granted
SG	10201701859T		Pending
WO	PCT/US2009/047031		Inactive

EXHIBIT 16

Mo-99 Technology Development

2017 Mo-99 Topical Meeting

Sept. 10-13, 2017 — Montreal Marriott Chateau Champlain, Montreal, QC Canada

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Mo-99 2017 - Technical Program
Document Status: Preliminary. May be subject to change.
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The overall Topical Meeting schedule is as follows:

- **September 10:** Registration (4:30 – 6 p.m.) and Welcome Reception (6 – 8 p.m.)
- **September 11-13:** Meeting Sessions
- **September 13:** Technical tour of the École Polytechnique de Montréal SLOWPOKE-2 Research Reactor and Thermal-hydraulic Laboratory . The reactor was converted from operation with highly enriched uranium fuel to low enriched uranium in 1997. Buses will depart the Montreal Marriott Hotel around 2 pm and return to the hotel by 5:30 pm. *Participation is limited to the first 80 persons.*
- **September 14:** Technical tour of the Jubilant DraxImage Inc. I-131 solutions/capsules, I-131 mIBG and Rb-82 generator manufacturing at its site in Montreal. “Jubilant DraxImage Inc. (a wholly-owned subsidiary of Jubilant Pharma) is a Nuclear Medicine company that develops, manufactures and commercializes radiopharmaceuticals used for the diagnosis, treatment and monitoring of disease.” Buses will depart the Montreal Marriott hotel at 8:30 am and return to the hotel around noon. **Tour is full.**

Questions?

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Mo-99 2017 News:

Nov. 21, 2017 — **Mo-99 2017 Abstracts and Presentations now available:** Mo-99 2017 abstracts and papers are now available for download… View »

May 05, 2017 —**Mo-99 2017 Announced:** Mo-99 2017 will be held in Montreal, QC Canada, September 10-13, 2017.

For more information:

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HOST: National Nuclear Security Administration

ORGANIZER: Argonne NATIONAL LABORATORY

Last updated:
08/30/17

EXHIBIT 17

Exhibit No. 17

Bracco's infringement charts are exemplary in nature and not intended to be limiting. As explained herein, the Ruby-Fill Rubidium Elution System infringes the claims of the '826 patent literally or under the doctrine of equivalents. However, nothing in this chart is meant to preclude that any claim element is infringed literally or, alternatively, at a minimum under the doctrine of equivalents (even for any elements where doctrine of equivalents is not specifically identified). Bracco reserves all rights with respect to its infringement contentions that will be submitted during the Investigation and may depend on any claim construction Respondents newly raise.

Claim 1 of the '826 Patent	Infringement Evidence
1. A method of building an infusion system to deliver a rubidium radioactive eluate comprising:	Jubilant makes, uses, offers to sell, sells, and/or imports an infusion system to deliver a rubidium radioactive eluate. Namely the Ruby-Fill System. RUBY RUBIDIUM ELUTION SYSTEM Manufacturer Jubilant DraxImage Inc. 16751 Trans-Canada Highway Kirkland, Québec Canada H9H 4J4 (514) 630-7080 *See* Exhibit No. 21 at 4. Jubilant submitted an application to the U.S. Food and Drug Administration on June 18, 2010 to market a purported equivalent version of CardioGen-82. Exhibit 20. Jubilant represented to the FDA that the RUBY-FILL system is a "pharmaceutical equivalent" to Bracco's CardioGen-82. *Id*.

Claim 1 of the ’826 Patent	Infringement Evidence
(a) installing a first shielding compartment, a second shielding compartment, and a shielded well on a platform of a cart, wherein:	Jubilant does and will install a first shielding compartment, a second shielding compartment, and a shielded well on a platform of a cart when manufacturing the Ruby-Fill system.  *See* Exhibit No. 21 at 1;

Claim 1 of the '826 Patent	Infringement Evidence

3.1 RUBY-FILL® RUBIDIUM RB 82 GENERATOR

The Generator always remains inside 1-inch-thick lead shielding. The handle must be removed before the lead cover can be removed. When the cover of the lead container is removed, only the fittings are exposed (see Fig. 3, Generator, Generator Handle & Lead Cover), which allows connection to the RUBY SET via the RUBY CONNECTORS. The Generator is a closed system and has Quick-Connect fittings which are plugged with metal caps for shipping (see Fig. 4, Generator Metal Caps). The inlet to the Generator is the male Quick-Connect and the outlet to the generator is the female Quick-Connect (see RUBY SET Installation, section 6.5). Once the Generator is expired there is no need to recap the Quick Connect fittings on the Generator with the metal caps.

Figure 3, Generator, Generator Handle & Lead Cover

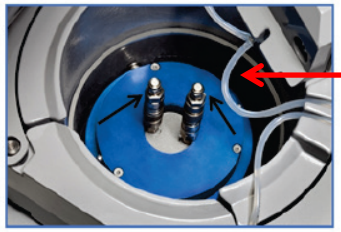


Figure 4, Generator Metal Caps

Id. at 10;

2.3 MAIN SYSTEM COMPONENTS

The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components):

1. Dose Calibrator
2. Waste Bottle
3. Pressure Transducer Holder and Connector
4. Pinch valves (four)
5. Photo Multiplier Tube (PMT)
6. Generator Well
7. Peristaltic Pump
8. Touch Screen Computer User Interface (not shown)
9. Removable Storage Compartment (not shown)

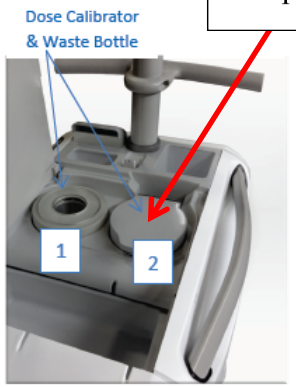


Figure 1, RUBY Rubidium Elution System

Id. at 9;

Claim 1 of the '826 Patent	Infringement Evidence

3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE

The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).

Figure 7, Waste Bottle in Waste Well

Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO).

Id. at 12;

2.3 MAIN SYSTEM COMPONENTS

The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components):

1. Dose Calibrator
2. Waste Bottle
3. Pressure Transducer Holder and Connector
4. Pinch valves (four)
5. Photo Multiplier Tube (PMT)
6. Generator Well
7. Peristaltic Pump
8. Touch Screen Computer User Interface (not shown)
9. Removable Storage Compartment (not shown)

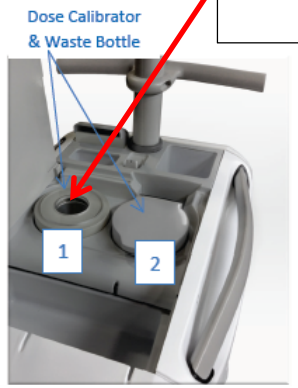
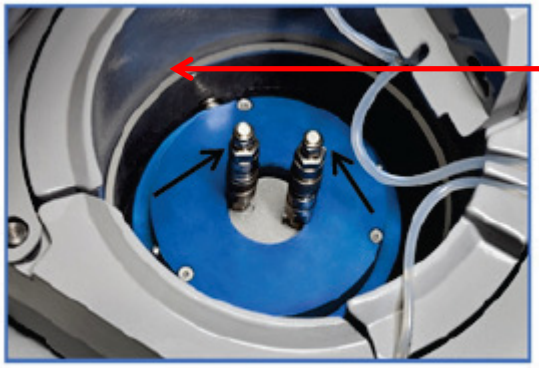


Figure 1, RUBY Rubidium Elution System

Id. at 9.

Claim 1 of the '826 Patent	Infringement Evidence
(i) the first shielding compartment has a first opening facing vertically upwardly,	The first shielding compartment of the Ruby-Fill system has a first opening facing vertically upwardly.  Figure 4, Generator Metal Caps *Id*. at 10.
(ii) the first opening is configured for a strontium-rubidium radioisotope generator to be inserted into and removed from the first shielding compartment,	The first opening of the Ruby-Fill system is configured for a strontium-rubidium radioisotope generator to be inserted into and removed from the first shielding compartment.

Claim 1 of the ’826 Patent	Infringement Evidence

6.6 INSTALLING THE NEW GENERATOR

Using the Generator handle, install a new Generator by inserting it carefully into the Generator well (see Fig. 37, Installing the New Generator). Remove the Generator handle, then the cover. Using aseptic techniques, remove the metal caps on the Generator and connect both RUBY CONNECTORS to the quick connects on the Generator, mating a male to a female quick connect. Make sure the tubing lines are in the grooves of the Generator lead well and close the Generator well lid promptly to avoid unnecessary exposure. The Generator packing slip is shipped with the Generator in a plastic pouch inside of the shipping container. Retrieve the packing slip, and on the Generator Setup screen, **step 5 under the Generator Installation and Setup** (Fig. 38, Generator Setup Screen) enter the lot number, strontium ratio (Sr-85/Sr-82), calibration date and expiration date.

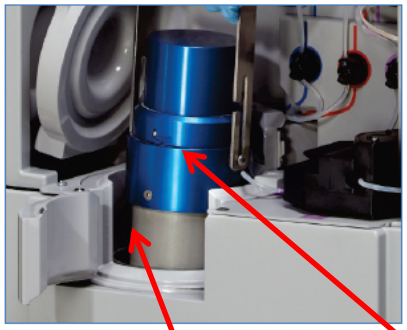


Figure 37, Installing the New Generator

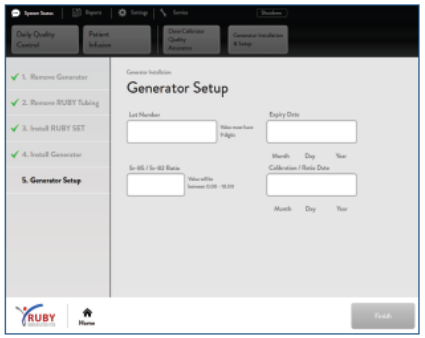


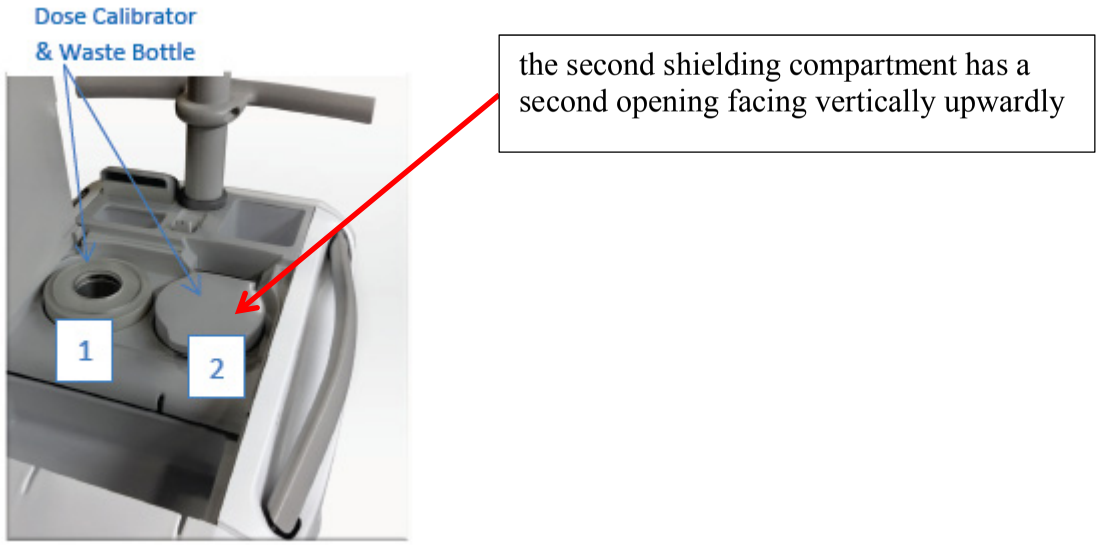
Figure 38, Generator Setup Screen

Save the Generator handle and cover with shipping container for use when removing the expired Generator and metal caps to recap the generator.

Id. at 34.

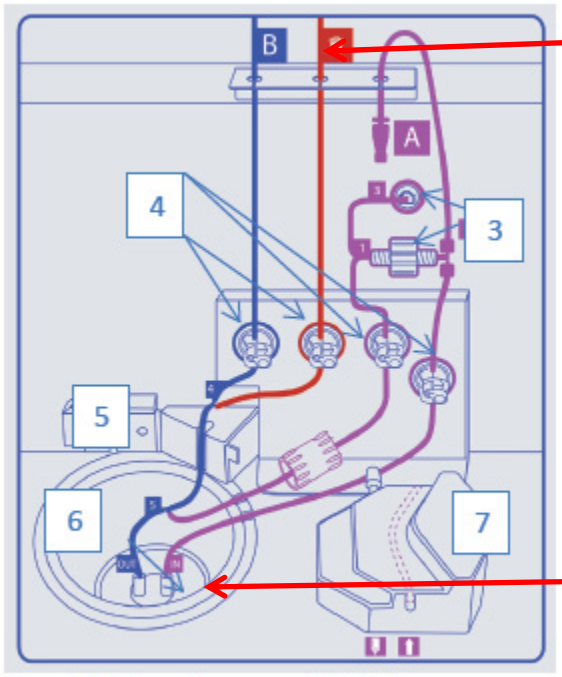
the first opening is configured for a strontium-rubidium radioisotope generator to be inserted into and removed from the first shielding compartment

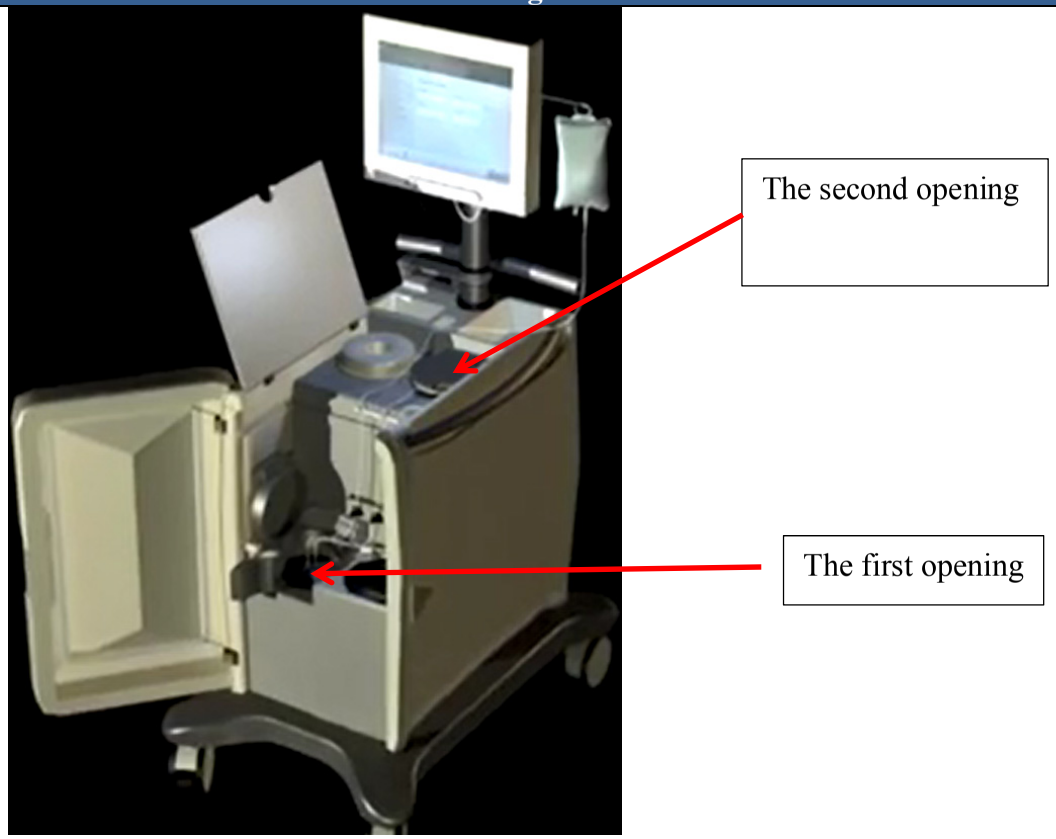
a strontium-rubidium radioisotope generator

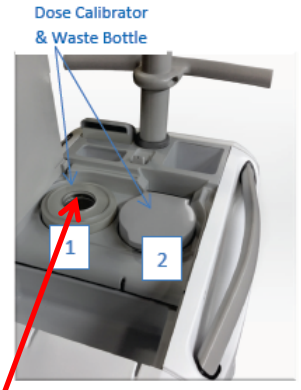
Claim 1 of the '826 Patent	Infringement Evidence
(iii) the second shielding compartment has a second opening facing vertically upwardly,	The second shielding compartment of the Ruby-Fill system has a second opening facing vertically upwardly.  Figure 1, RUBY Rubidium Elution System *Id*. at 9;

Claim 1 of the ’826 Patent	Infringement Evidence
	 Figure 7. Waste Bottle in Waste Well *Id*. at 12.

Claim 1 of the '826 Patent	Infringement Evidence
(iv) the second opening is configured for a waste bottle to be inserted into and removed from the second shielding compartment,	The second opening of the Ruby-Fill system is configured for a waste bottle to be inserted into and removed from the second shielding compartment. the second opening is configured for a waste bottle to be inserted into and removed from the second shielding compartment **3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE** The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).  A waste bottle Figure 7, Waste Bottle in Waste Well Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO). *Id*. at 12.

Claim 1 of the '826 Patent	Infringement Evidence
(v) the first opening is located at a lower elevation than the second opening, and	The first opening of the Ruby-Fill system is located at a lower elevation than the second opening.  Figure 2, System Components (#3-#7) *Id*. at 9;

Claim 1 of the ’826 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1.

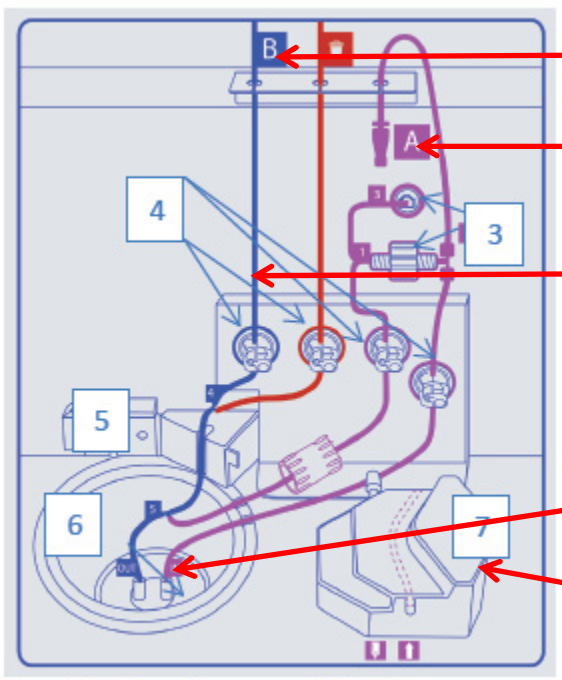
Claim 1 of the '826 Patent	Infringement Evidence
(vi) the shielded well is configured to receive an eluate reservoir that is configured to receive a sample of the rubidium radioactive eluate;	The shielded well of the Ruby-Fill system is configured to receive an eluate reservoir that is configured to receive a sample of the rubidium radioactive eluate. **2.3 MAIN SYSTEM COMPONENTS** The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components): 1. Dose Calibrator 2. Waste Bottle 3. Pressure Transducer Holder and Connector 4. Pinch valves (four) 5. Photo Multiplier Tube (PMT) 6. Generator Well 7. Peristaltic Pump 8. Touch Screen Computer User Interface (not shown) 9. Removable Storage Compartment (not shown)  Figure 1, RUBY Rubidium Elution System the shielded well is configured to receive an eluate reservoir that is configured to receive a sample of the rubidium radioactive eluate Exhibit No. 21 at 9;

Claim 1 of the ’826 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *See, e.g., id.* at 42.

Claim 1 of the '826 Patent	Infringement Evidence
(b) configuring a computer with a touch screen display for the infusion system to:	The Ruby-Fill system has a computer with a touch screen display for the infusion system.  *Id.* at 1;

Claim 1 of the '826 Patent		Infringement Evidence
		2.2 SYSTEM DESCRIPTION The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions. The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message. *Id*. at 8.
(i)	fill the eluate reservoir in the shielded well on-board the cart with the sample of the rubidium radioactive eluate by pumping saline from a saline reservoir into the strontium-rubidium radioisotope generator via a saline tubing line thereby generating the rubidium radioactive eluate that is discharged through an eluate tubing line,	The Ruby-Fill system can be configured to fill the eluate reservoir in the shielded well on-board the cart with the sample of the rubidium radioactive eluate by pumping saline from a saline reservoir into the strontium-rubidium radioisotope generator via a saline tubing line thereby generating the rubidium radioactive eluate that is discharged through an eluate tubing line.

Claim 1 of the '826 Patent	Infringement Evidence



to eluate reservoir in the shielded well on-board the cart

from a saline reservoir

an eluate tubing line

strontium-rubidium radioisotope generator

a pump for pumping saline from a saline reservoir into the strontium-rubidium radioisotope generator via a saline tubing line

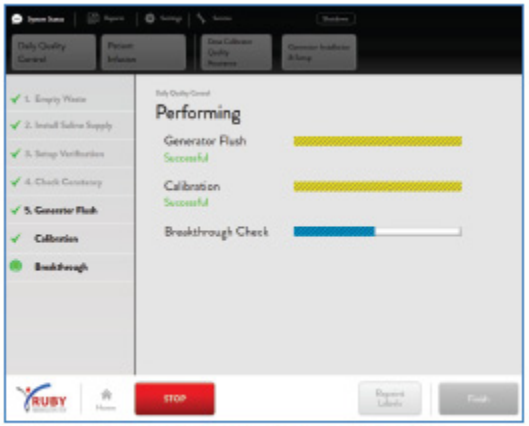
Figure 2, System Components (#3-#7)

Id. at 9;

6.1 DOSE CALIBRATOR QUALITY ASSURANCE

The RUBY Rubidium Elution System comes with an integrated dose calibrator. This dose calibrator is fully controlled using the system's software. To access the quality assurance mode, press Dose Calibrator Quality Assurance on the second row of the task bar and enter the required password. The control screen is displayed (see Fig. 26, Dose Calibrator Quality Assurance Screen). To perform the required quality assurance tests, such as Linearity, Geometry and Accuracy, an independent control screen is included to enable the operation and/or configuration of the dose calibrator in conventional mode (Table 2, Dose Calibrator Quality Assurance & Required Frequency of Performance). JDI personnel will complete all four quality assurance tests upon installation of the elution system. Users are responsible for performing Constancy daily (integrated into Daily Quality Control); Linearity quarterly and Accuracy annually.

Claim 1 of the '826 Patent		Infringement Evidence
		Id. at 28; The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id*. at 42.
(ii)	determine a strontium breakthrough test result on the sample of the rubidium radioactive eluate filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, and	The Ruby-Fill system can be configured to determine a strontium breakthrough test result on the sample of the rubidium radioactive eluate filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart.

Claim 1 of the '826 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id*. at 42.  Figure 49, Flush, Calibration, and Breakthrough Screen  Figure 50, Performing Daily Quality Control (Flush and Calibration are completed and the Breakthrough Check is in progress) *Id*. at 43.

<table>
<tr><th>Claim 1 of the ’826 Patent</th><th>Infringement Evidence</th></tr>
<tr><td>(iii) not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.</td><td>
The Ruby-Fill system can be configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.
<table>
<tr><th>System Error Message</th><th>Message Meaning</th><th>How to Troubleshoot</th></tr>
<tr><td>Sr Breakthrough Too High</td><td>The breakthrough limit level is reached. Patient infusions not allowed.</td><td>▪ Verify that the generator is not expired.
▪ Verify background activity fluctuations.
▪ Repeat radioactivity calibration and breakthrough check.
▪ Install a new generator.</td></tr>
</table>
Id. at 59;

The system can be used with four (4) patients before a Quality Control procedure must be performed if the breakthrough reaches an alert limit. If the user repeats the flush, the system counts this as a patient infusion.

≥ 50% of the USP limit* (see Table 3), the system does not allow the user to perform a patient infusion.
Refer to Table 3 below for instructions to follow on Strontium Breakthrough results.

<table>
<tr><th>PASS
< 20% of USP limits*
(Green)</th><th>ALERT
≥ 20% and <50% of USP limits*
OR 20L volume limit
(Yellow)</th><th>FAIL
≥ 50% of USP limits*
OR 30L volume limit
(Red)</th></tr>
<tr><td>Breakthrough level is low.</td><td>Breakthrough level is increased.</td><td>Breakthrough level is approaching the allowable limit.</td></tr>
<tr><td>The Daily Quality Procedure (automated breakthrough test) is valid for a 24 hour period.</td><td>The Daily Quality Procedure (automated breakthrough test) is valid for 4 patients only.</td><td>The Daily Quality Control (automated breakthrough test) does not allow a sufficient margin of safety to continue the elutions (scans).</td></tr>
<tr><td>Proceed with use</td><td>Repeat an automated Daily Quality Control after every 4 patients (8 scans) and record the results
Contact Jubilant DraxImage:
1-888-633-5343</td><td>The use of the RUBY-FILL® Rubidium Rb 82 Generator must be discontinued immediately.
Contact Jubilant DraxImage:
1-888-633-5343</td></tr>
<tr><td colspan="3">*USP limits: <0.02μCi of Sr-82/mCi of Rb-82; <0.2μCi of Sr-85/mCi of Rb-82</td></tr>
</table>
Table 3: Strontium Breakthrough Results

Id. at 44.
</td></tr>
</table>

EXHIBIT 18

Exhibit No. 18

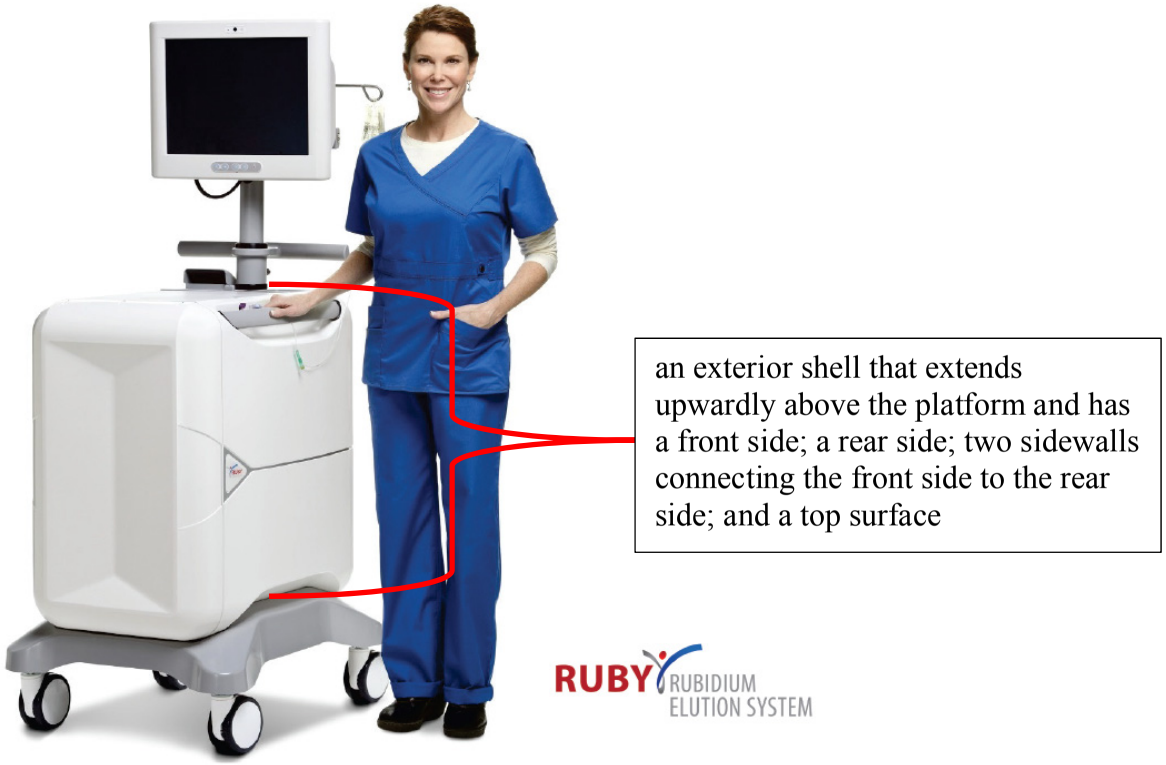
Bracco's infringement charts are exemplary in nature and not intended to be limiting. As explained herein, the Ruby-Fill Rubidium Elution System infringes the claims of the '869 patent literally or under the doctrine of equivalents. However, nothing in this chart is meant to preclude that any claim element is infringed literally or, alternatively, at a minimum under the doctrine of equivalents (even for any elements where doctrine of equivalents is not specifically identified). Bracco reserves all rights with respect to its infringement contentions that will be submitted during the Investigation and may depend on any claim construction Respondents newly raise.

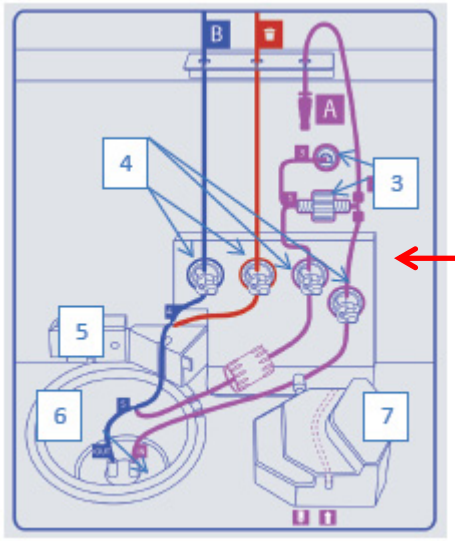
Claim 1 of the '869 Patent	Infringement Evidence
1. An infusion system on-board a cart comprising:	Jubilant makes, uses, offers to sell, sells, and/or imports into the United States manufactures an infusion system on-board a cart. Namely the Ruby-Fill System.  Exhibit No. 21 at 1;

Claim 1 of the '869 Patent	Infringement Evidence
	2.2 SYSTEM DESCRIPTION The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. *Id*. at 8. Jubilant submitted an application to the U.S. Food and Drug Administration on June 18, 2010 to market a purported equivalent version of CardioGen-82. Exhibit 20. Jubilant represented to the FDA that the Ruby-Fill system is a "pharmaceutical equivalent" to Bracco's CardioGen-82. *Id*.

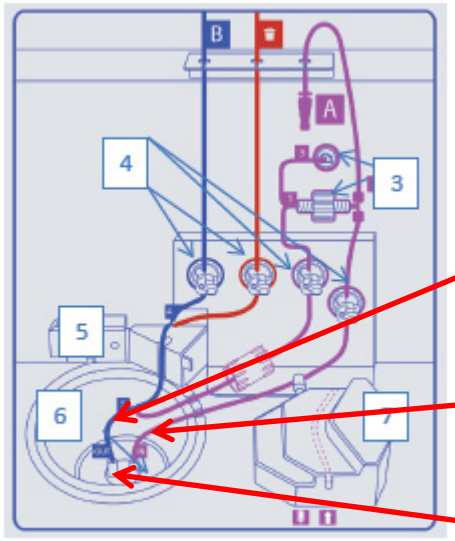
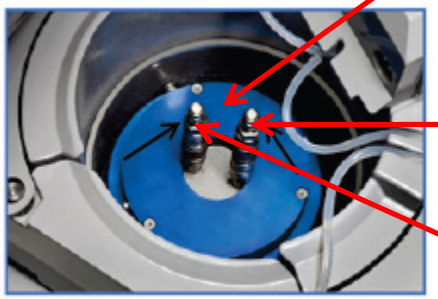
Claim 1 of the '869 Patent	Infringement Evidence
(a) a cabinet structure that comprises:	The Ruby-Fill infusion system has a cabinet structure.  Exhibit No. 21 at 1.

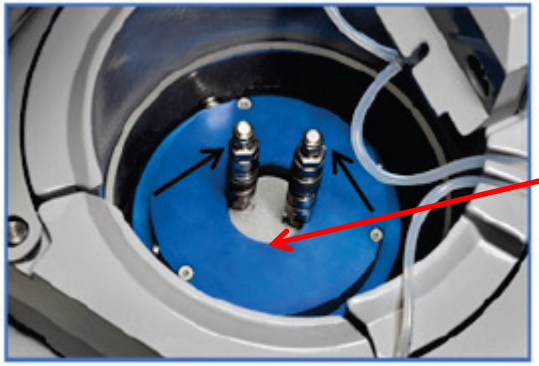
Claim 1 of the ’869 Patent	Infringement Evidence
(i) a platform,	The cabinet structure of the Ruby-Fill infusion system has a platform.  *Id*. at 1.

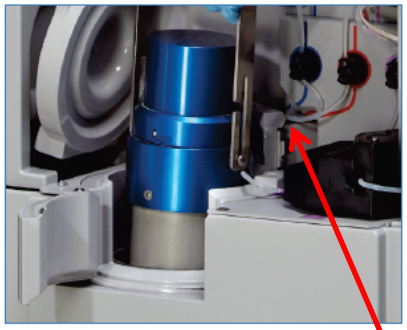
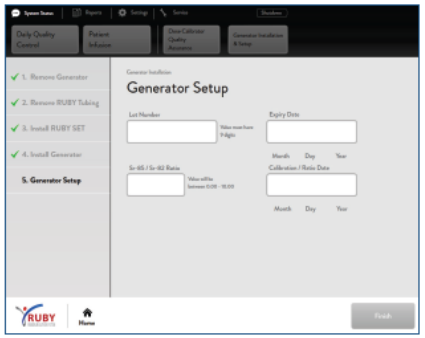
Claim 1 of the '869 Patent	Infringement Evidence
(ii) an exterior shell that extends upwardly above the platform and has a front side; a rear side; two sidewalls connecting the front side to the rear side; and a top surface; wherein the platform and the exterior shell collectively define an interior space of the cabinet structure and wherein the interior space of the cabinet structure is configured to receive a strontium-rubidium radioisotope generator having an inlet tubing port configured to receive saline and an outlet tubing port configured to discharge a rubidium radioactive eluate,	The cabinet structure of the Ruby-Fill infusion system has an exterior shell that extends upwardly above the platform and has a front side; a rear side; two sidewalls connecting the front side to the rear side; and a top surface.  *Id.* at 1;

Claim 1 of the '869 Patent	Infringement Evidence
	The platform and the exterior shell collectively define an interior space of the cabinet structure of the Ruby-Fill infusion system.  Figure 2, System Components (#3–#7) *See e.g., id.* at 9;

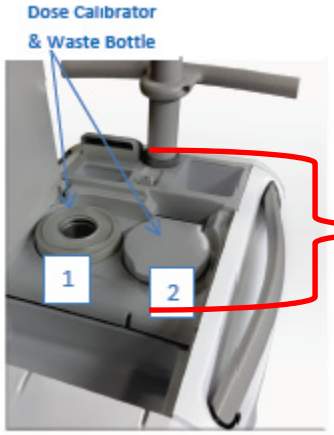
Claim 1 of the ’869 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1;

Claim 1 of the '869 Patent	Infringement Evidence
	The interior space of the cabinet structure of the Ruby-Fill infusion system is configured to receive a strontium-rubidium radioisotope generator having an inlet tubing port configured to receive saline and an outlet tubing port configured to discharge a rubidium radioactive eluate.  Figure 2, System Components (#3-#7) Exhibit No. 21 at 9;  Figure 4, Generator Metal Caps *Id*. at 10.

Claim 1 of the '869 Patent	Infringement Evidence
(iii) an opening through the exterior shell configured to provide access to the strontium-rubidium radioisotope generator within the interior space of the cabinet structure, and	The cabinet structure of the Ruby-Fill infusion system has an opening through the exterior shell configured to provide access to the strontium-rubidium radioisotope generator within the interior space of the cabinet structure.  the strontium-rubidium radioisotope generator within the interior space of the cabinet structure Figure 4, Generator Metal Caps *Id*. at 10;

Claim 1 of the '869 Patent	Infringement Evidence
	6.6 INSTALLING THE NEW GENERATOR Using the Generator handle, install a new Generator by inserting it carefully into the Generator well (see Fig. 37, Installing the New Generator). Remove the Generator handle, then the cover. Using aseptic techniques, remove the metal caps on the Generator and connect both RUBY CONNECTORS to the quick connects on the Generator, mating a male to a female quick connect. Make sure the tubing lines are in the grooves of the Generator lead well and close the Generator well lid promptly to avoid unnecessary exposure. The Generator packing slip is shipped with the Generator in a plastic pouch inside of the shipping container. Retrieve the packing slip, and on the Generator Setup screen, **step 5 under the Generator Installation and Setup** (Fig. 38, Generator Setup Screen) enter the lot number, strontium ratio (Sr-85/Sr-82), calibration date and expiration date.  Figure 37, Installing the New Generator  Figure 38, Generator Setup Screen Save the Generator handle and cover with shipping container for use when removing the expired Generator and metal caps to recap the generator. an opening through the exterior shell *Id*. at 34;

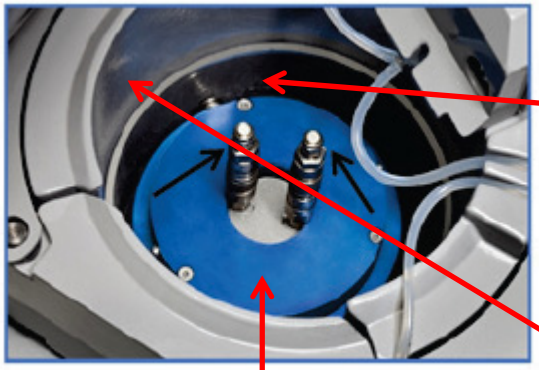
Claim 1 of the ’869 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1.

Claim 1 of the '869 Patent	Infringement Evidence
(iv) an opening through the top surface of the exterior shell configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure;	The cabinet structure of the Ruby-Fill infusion system has an opening through the top surface of the exterior shell configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure.  Figure 1, RUBY Rubidium Elution System an opening through the top surface of the exterior shell configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure Exhibit No. 21 at 9;

Claim 1 of the '869 Patent	Infringement Evidence
	3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).  Figure 7, Waste Bottle in Waste Well Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO). a waste bottle *Id*. at 12.

Claim 1 of the '869 Patent	Infringement Evidence
(b) a computer with a touch screen display configured to receive an input from a user for controlling operation of the infusion system, wherein the touch screen display is mounted on a vertical post having a top end extending above the cabinet structure;	The Ruby-Fill system has a computer with a touch screen display configured to receive an input from a user for controlling operation of the infusion system, wherein the touch screen display is mounted on a vertical post having a top end extending above the cabinet structure.  *Id.* at 1;

Claim 1 of the '869 Patent	Infringement Evidence
	2.2 SYSTEM DESCRIPTION The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions. The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message. *Id*. at 8.

Claim 1 of the '869 Patent	Infringement Evidence
(c) a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment;	The Ruby-Fill system has a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment  Figure 4, Generator Metal Caps a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment a first opening facing vertically upwardly the strontium-rubidium radioisotope generator *Id*. at 10;

Claim 1 of the '869 Patent	Infringement Evidence

6.6 INSTALLING THE NEW GENERATOR

Using the Generator handle, install a new Generator by inserting it carefully into the Generator well (see Fig. 37, Installing the New Generator). Remove the Generator handle, then the cover. Using aseptic techniques, remove the metal caps on the Generator and connect both RUBY CONNECTORS to the quick connects on the Generator, mating a male to a female quick connect. Make sure the tubing lines are in the grooves of the Generator lead well and close the Generator well lid promptly to avoid unnecessary exposure. The Generator packing slip is shipped with the Generator in a plastic pouch inside of the shipping container. Retrieve the packing slip, and on the Generator Setup screen, **step 5 under the Generator Installation and Setup** (Fig. 38, Generator Setup Screen) enter the lot number, strontium ratio (Sr-85/Sr-82), calibration date and expiration date.

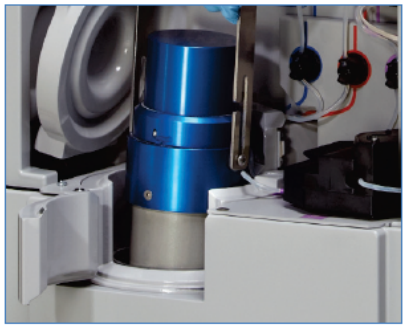


Figure 37, Installing the New Generator

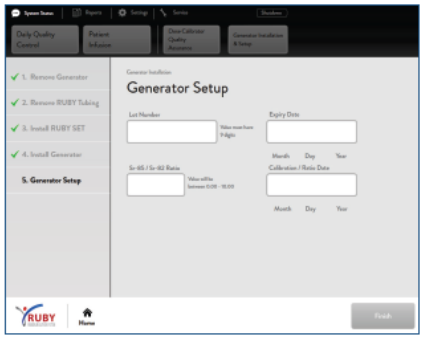
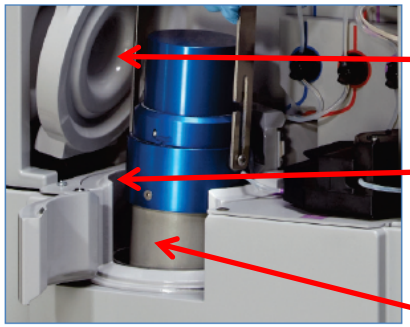
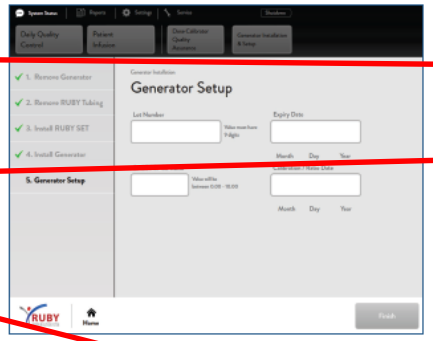


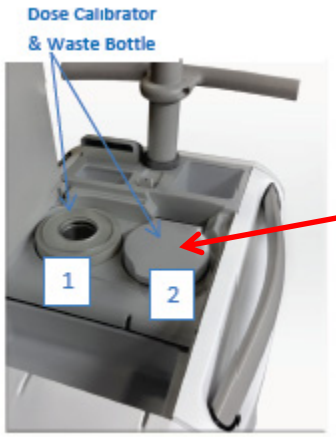
Figure 38, Generator Setup Screen

Save the Generator handle and cover with shipping container for use when removing the expired Generator and metal caps to recap the generator.

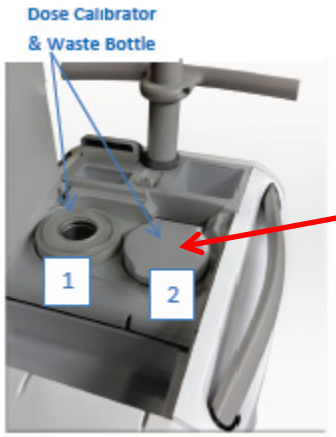
Id. at 34.

Claim 1 of the '869 Patent	Infringement Evidence
(d) a first door accessible via the opening through the exterior shell, the first door being configured to provide access to the first shielding compartment and to close over the first opening;	The Ruby-Fill system has a first door accessible via the opening through the exterior shell, the first door being configured to provide access to the first shielding compartment and to close over the first opening. **6.6 INSTALLING THE NEW GENERATOR** Using the Generator handle, install a new Generator by inserting it carefully into the Generator well (see Fig. 37, Installing the New Generator). Remove the Generator handle, then the cover. Using aseptic techniques, remove the metal caps on the Generator and connect both RUBY CONNECTORS to the quick connects on the Generator, mating a male to a female quick connect. Make sure the tubing lines are in the grooves of the Generator lead well and close the Generator well lid promptly to avoid unnecessary exposure. The Generator packing slip is shipped with the Generator in a plastic pouch inside of the shipping container. Retrieve the packing slip, and on the Generator Setup screen, step 5 under the Generator Installation and Setup (Fig. 38, Generator Setup Screen) enter the lot number, strontium ratio (Sr-85/Sr-82), calibration date and expiration date.  Figure 37, Installing the New Generator  Figure 38, Generator Setup Screen *Id*. at 34;

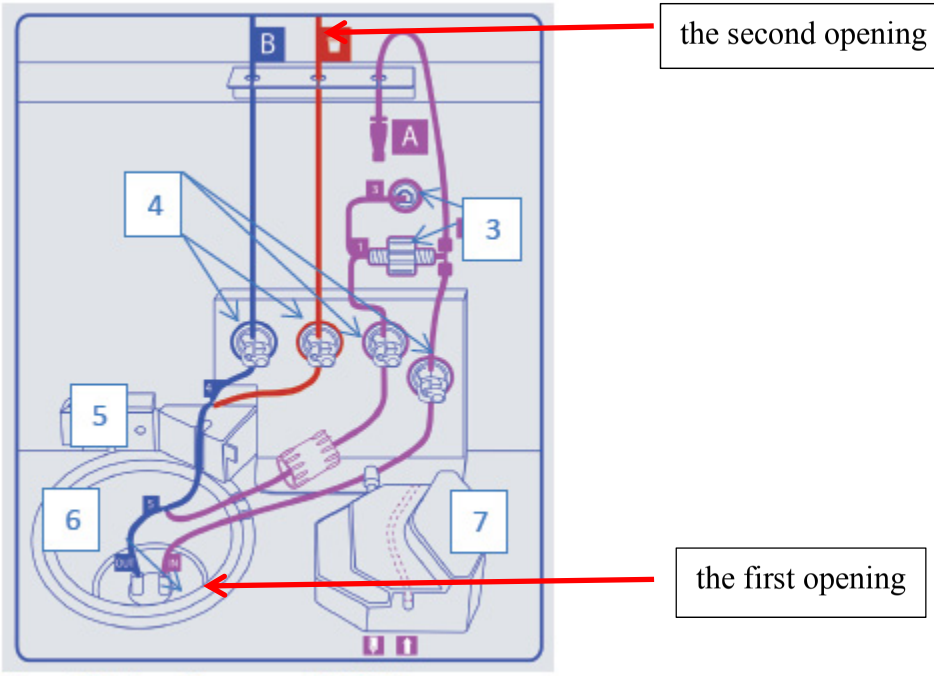
Claim 1 of the '869 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1.

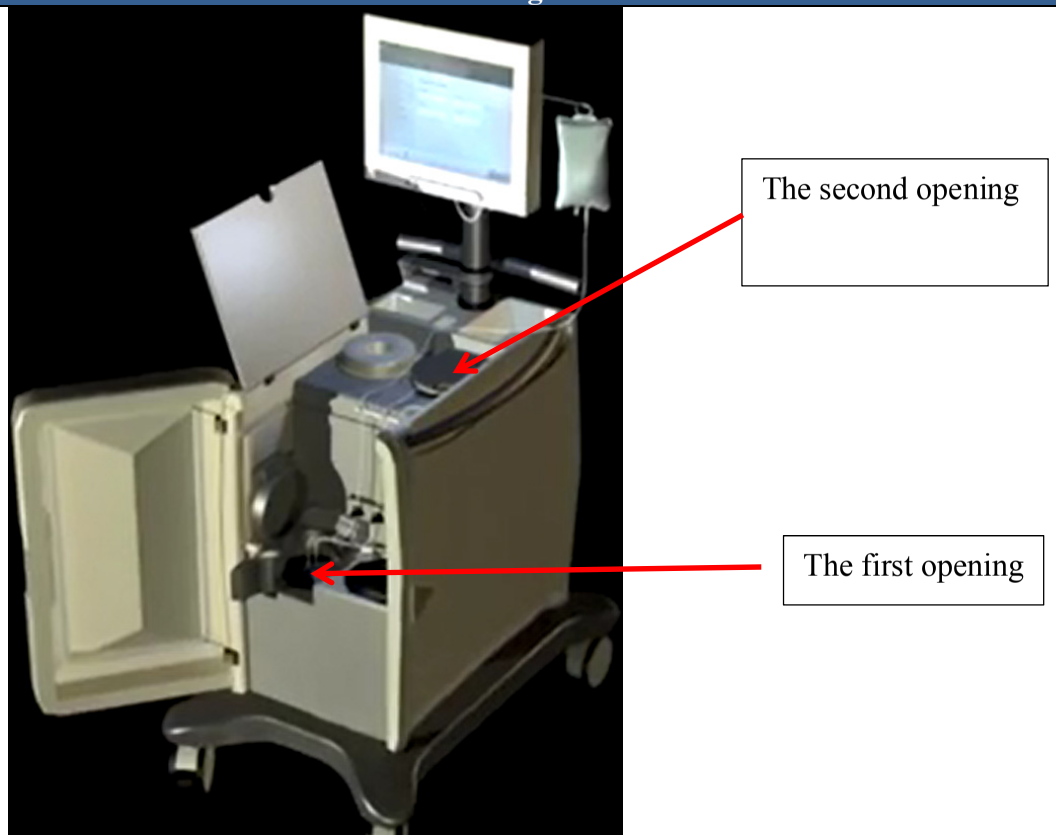
Claim 1 of the '869 Patent	Infringement Evidence
(e) a second shielding compartment having a second opening facing vertically upwardly through which the waste bottle can be inserted into and removed from the second shielding compartment;	The Ruby-Fill system has a second shielding compartment having a second opening facing vertically upwardly through which the waste bottle can be inserted into and removed from the second shielding compartment.  Figure 1, RUBY Rubidium Elution System a second shielding compartment having a second opening facing vertically upwardly through which the waste bottle can be inserted into and removed from the second shielding compartment Exhibit No. 21 at 9;

Claim 1 of the '869 Patent	Infringement Evidence
	3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).  Figure 7, Waste Bottle in Waste Well Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO). the waste bottle can be inserted into and removed from the second shielding compartment *Id*. at 12.

Claim 1 of the '869 Patent	Infringement Evidence
(f) a second door accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening;	The Ruby-Fill system has a second door accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening.  Figure 1, RUBY Rubidium Elution System a second door accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening *Id*. at 9;

Claim 1 of the '869 Patent	Infringement Evidence
	3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).  Figure 7, Waste Bottle in Waste Well Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO). a second door . *Id*. at 12.

Claim 1 of the '869 Patent	Infringement Evidence
(g) wherein the first opening is located at a lower elevation than the second opening;	The Ruby-Fill system's first opening is located at a lower elevation than the second opening.  Figure 2, System Components (#3-#7) *Id*. at 9;

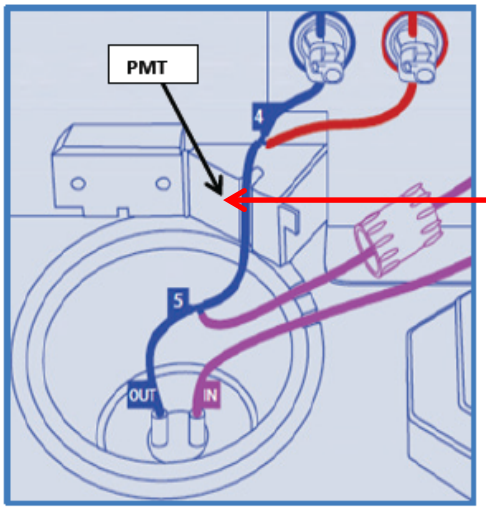
Claim 1 of the '869 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1.
(h) a radioactivity detector positioned to measure radioactivity of the rubidium radioactive eluate flowing through an eluate tubing line in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator;	The Ruby-Fill system has a radioactivity detector positioned to measure radioactivity of the rubidium radioactive eluate flowing through an eluate tubing line in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator.

Claim 1 of the '869 Patent	Infringement Evidence

System Error Message	Message Meaning	How to Troubleshoot
Radioactivity Counter Overlight	The radioactivity counter is exposed to light	▪ Verify that the radioactivity counter cover is closed.
Radioactivity Counter Failure	Error detected from the radioactivity counter	▪ Verify that the radioactivity counter cover is closed. ▪ Restart the system.
Radioactivity Counter Disconnected	Communication failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.
Radioactivity Counter Error	System detected a failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.
Radioactivity Counter Initialization Error	System detected a failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.

Exhibit No. 21 at 59;

12. Insert line section between #4 and #5 into groove of the PMT, ensuring PMT door may be closed properly after tube placement (See Fig. 33, Installation of PMT portion of RUBY SET).



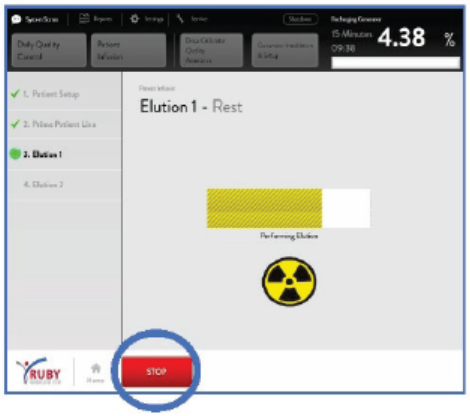
a radioactivity detector positioned to measure radioactivity of the rubidium radioactive eluate flowing through an eluate tubing line in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator

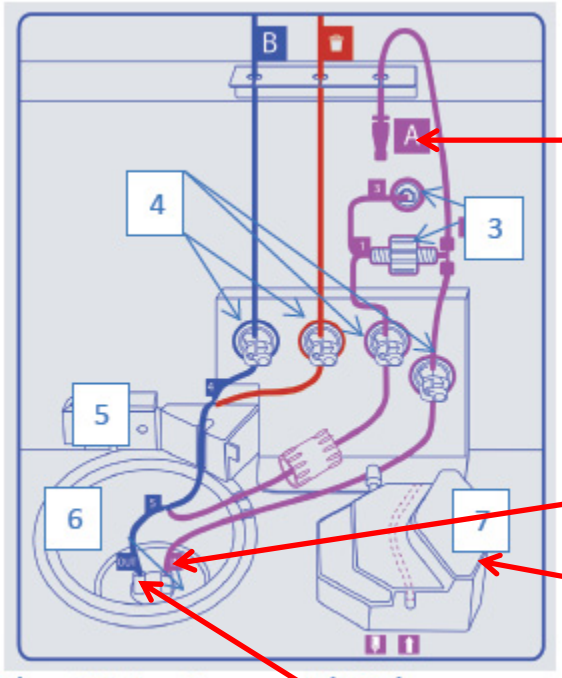
Figure 33, Installation of PMT portion of RUBY SET

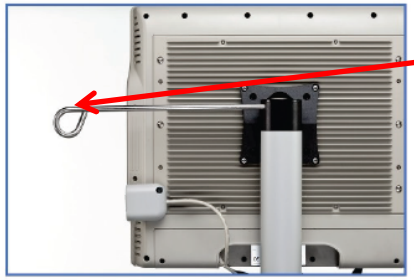
Id. at 32.

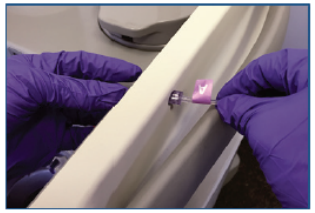
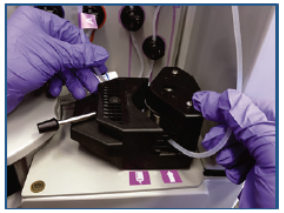
Claim 1 of the '869 Patent	Infringement Evidence
(i) a shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample; and	The Ruby-Fill system has a shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample. **2.3 MAIN SYSTEM COMPONENTS** The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components): 1. Dose Calibrator 2. Waste Bottle 3. Pressure Transducer Holder and Connector 4. Pinch valves (four) 5. Photo Multiplier Tube (PMT) 6. Generator Well 7. Peristaltic Pump 8. Touch Screen Computer User Interface (not shown) 9. Removable Storage Compartment (not shown)  Figure 1, RUBY Rubidium Elution System a shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample *Id*. at 9;

Claim 1 of the '869 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *See, e.g., id.* at 42 (shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample).
(j) wherein the computer of the infusion system is configured to:	The Ruby-Fill system has a computer for the infusion system. **2.2 SYSTEM DESCRIPTION** The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions. The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message. *Id.* at 8.

Claim 1 of the '869 Patent	Infringement Evidence
(i) provide a stop button on the touch screen display to abort a function of the infusion system in response to a user input activating the stop button,	The Ruby-Fill's computer can be configured to provide a stop button on the touch screen display to abort a function of the infusion system in response to a user input activating the stop button. **4.6 EMERGENCY TERMINATION OF PROCEDURE** The RUBY Rubidium Elution System has an emergency **Stop** button on the computer monitor screen that is available at any time during any function (see Fig. 8, Emergency Stop Button). If sudden termination of a procedure is necessary, press **Stop** and the pump will halt and all pinch valves will close. The patient can then be disconnected safely from the elution system until the situation is resolved. No modification of this equipment is allowed. The system including the RUBY-FILL® Rubidium Rb 82 Generator should only be used by authorized trained personnel and in accordance with its intended use. Clicking on the RUBY logo takes the user to a tool that recalibrates the PC Monitor. Refer to the **Troubleshooting** section for additional information about this tool.  Figure 8, Emergency Stop Button *Id*. at 15.

Claim 1 of the '869 Patent	Infringement Evidence
(ii) pump saline from a saline reservoir positioned outside of the interior space of the cabinet structure into the strontium-rubidium radioisotope generator through the inlet tubing port of the strontium-rubidium radioisotope generator thereby generating the rubidium radioactive eluate that is discharged through the outlet tubing port,	The Ruby-Fill's computer can be configured to pump saline from a saline reservoir positioned outside of the interior space of the cabinet structure into the strontium-rubidium radioisotope generator through the inlet tubing port of the strontium-rubidium radioisotope generator thereby generating the rubidium radioactive eluate that is discharged through the outlet tubing port.  Figure 2, System Components (#3-#7) *Id.* at 9;

Claim 1 of the ’869 Patent	Infringement Evidence
	3.4 SALINE BAGS, RUBY SALINE LINES, RUBY IV LINES A bag of sterile 0.9% sodium chloride (additive free) injection, USP bag is installed by the user on the elution system to elute the generator. The saline bag hangs from a specially designed hook behind the computer screen (see Fig. 6, Saline Hook).  Figure 6, Saline Hook The RUBY SALINE LINE connects the saline bag to the RUBY SET. The RUBY SALINE LINE is installed by the user through the pump in the elution system and is aseptically connected to the ”A” end of the RUBY SET via a luer-lock connection (RUBY SALINE LINE Installation, section 6.7). The RUBY SET terminates with a Luer-Lock fitting, ”B” where the RUBY IV LINE is connected. An important feature of the RUBY IV LINE is an integrated 0.22 micron vented filter for increased patient safety (RUBY IV LINE Installation, section 6.8) saline reservoir positioned outside of the interior space of the cabinet structure *Id*. at 11;

Claim 1 of the ’869 Patent	Infringement Evidence
	6.7 INSTALLING THE 0.9% SODIUM CHLORIDE (ADDITIVE FREE) INJECTION, USP (SALINE SUPPLY) & RUBY SALINE LINE A 0.9% sodium chloride (additive free) injection USP saline bag, RUBY SALINE LINE and RUBY IV LINE must be installed by the user to perform the Setup Validation in Daily Quality Control tab on the touchscreen monitor. 1. Visually inspect the RUBY SALINE LINE packaging for damage. Discard if damaged. 2. Using aseptic techniques, remove protective cap from saline bag and spike saline bag with the spike end of the RUBY SALINE LINE. 3. Ensure that the roller clamp is in the closed position on the RUBY SALINE LINE and hang the saline bag on the Saline hook. 4. Insert the RUBY SALINE LINE into the RUBY Rubidium Elution System via the keyhole on the right hand side of the system (see Fig. 39, RUBY SALINE LINE keyhole). 5. Open the pump by pulling lever **and** install the RUBY SALINE LINE into the pump (see Fig. 40, Installing RUBY SALINE LINE into Pump). Close the pump using the lever. 6. Using aseptic techniques, remove the protective cap of the RUBY SALINE LINE at point A and connect to the A portion of the RUBY SET (see Fig. 41, Attaching RUBY SALINE LINE to RUBY SET). 7. Open roller clamp on the RUBY SALINE LINE. 8. On the touch screen, select Pre-set Saline Volume (500mL or 1000ml) or Customized Saline Volume. The 0.9% USP saline bag must contain more than 50mL. 9. Change RUBY SALINE LINE with each new install of saline supply.  Figure 39, RUBY SALINE LINE Keyhole  Figure 40, Installing RUBY SALINE LINE into Pump *Id*. at 35;

Claim 1 of the ’869 Patent	Infringement Evidence
	7.2 INSTALL SALINE SUPPLY Refer to INSTALLING THE 0.9% SODIUM CHLORIDE (ADDITIVE FREE) INJECTION, USP (SALINE SUPPLY) & RUBY SALINE IV LINE, section 6.7 (see Fig. 45, Install Saline Supply Screen).  Figure 45, Install Saline Supply Screen *Id*. at 39.

Claim 1 of the '869 Patent	Infringement Evidence
(iii) fill the eluate reservoir in the shielded well on-board the cart with the test sample of the rubidium radioactive eluate,	The Ruby-Fill's computer can be configured to fill the eluate reservoir in the shielded well on-board the cart with the test sample of the rubidium radioactive eluate. **2.3 MAIN SYSTEM COMPONENTS** The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components): 1. Dose Calibrator 2. Waste Bottle 3. Pressure Transducer Holder and Connector 4. Pinch valves (four) 5. Photo Multiplier Tube (PMT) 6. Generator Well 7. Peristaltic Pump 8. Touch Screen Computer User Interface (not shown) 9. Removable Storage Compartment (not shown)  Figure 1, RUBY Rubidium Elution System the shielded well on-board the cart with the test sample of the rubidium radioactive eluate *Id.* at 9;

Claim 1 of the '869 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *See, e.g., id.* at 42.

Claim 1 of the '869 Patent	Infringement Evidence
(iv) determine a strontium breakthrough test result on the test sample filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, and	The Ruby-Fill's computer can be configured to determine a strontium breakthrough test result on the test sample filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart. The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id*. at 42;

Claim 1 of the '869 Patent	Infringement Evidence

Figure 49, Flush, Calibration, and Breakthrough Screen

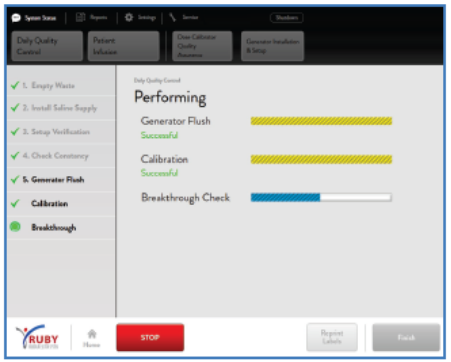


Figure 50, Performing Daily Quality Control (Flush and Calibration are completed and the Breakthrough Check is in progress)

The yellow progress bar indicates that a radioactive procedure is in progress and that radioactive solution is flowing through unshielded tubes. The user should remain at a safe distance from the elution system.

When the breakthrough check is complete, a label with the daily QC values automatically prints as configured in the settings. The user can either press Reprint Labels or press **Finish**.

When the user selects **Finish**, the Ready for Patient Infusion Screen appears (see Fig. 51, Ready for Patient Infusion Screen). This screen displays important information about the state of the elution system at a glance. The most important information displayed on this screen is:

- Breakthrough: Indicated as a percentage of the USP limit* (see Table 3), this field indicates the level of impurities calculated in the Daily Quality Control.
- Breakthrough History: The graph tracks the breakthrough levels for each day of use of the installed generator.
- Below the yellow line (<20% of USP limit*, see Table 3), the system can be used without any restriction on the number of infusions per Quality Control.
- An alert limit is reached when the reading is above the yellow line (≥ 20%) and below the red line (<50% of the USP limit*, see Table 3). Alert limits may be triggered by the following:
    - 20 L of saline eluted through the Generator.
    - or an eluate Sr-82 level of ≥0.004 µCi/mCi Rb-82. and ≤ 0.01 µCi/mCi Rb-82.
    - or an eluate Sr-85 level of ≥0.04 µCi/mCi and ≤ 0.1 µCi/mCi Rb-82.

Id. at 43.

<table>
<tr><th>Claim 1 of the ’869 Patent</th><th>Infringement Evidence</th></tr>
<tr><td>(v) not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.</td><td>
The Ruby-Fill’s computer can be configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.
<table>
<tr><th>System Error Message</th><th>Message Meaning</th><th>How to Troubleshoot</th></tr>
<tr><td>Sr Breakthrough Too High</td><td>The breakthrough limit level is reached. Patient infusions not allowed.</td><td>▪ Verify that the generator is not expired.
▪ Verify background activity fluctuations.
▪ Repeat radioactivity calibration and breakthrough check.
▪ Install a new generator.</td></tr>
</table>
Id. at 59;

The system can be used with four (4) patients before a Quality Control procedure must be performed if the breakthrough reaches an alert limit. If the user repeats the flush, the system counts this as a patient infusion.

• ≥ 50% of the USP limit* (see Table 3), the system does not allow the user to perform a patient infusion.
• Refer to Table 3 below for instructions to follow on Strontium Breakthrough results.
<table>
<tr><th>PASS
< 20% of USP limits*
(Green)</th><th>ALERT
≥ 20% and <50% of USP limits*
OR 20L volume limit
(Yellow)</th><th>FAIL
≥ 50% of USP limits*
OR 30L volume limit
(Red)</th></tr>
<tr><td>Breakthrough level is low.</td><td>Breakthrough level is increased.</td><td>Breakthrough level is approaching the allowable limit.</td></tr>
<tr><td>The Daily Quality Procedure (automated breakthrough test) is valid for a 24 hour period.</td><td>The Daily Quality Procedure (automated breakthrough test) is valid for 4 patients only.</td><td>The Daily Quality Control (automated breakthrough test) does not allow a sufficient margin of safety to continue the elutions (scans).</td></tr>
<tr><td>Proceed with use</td><td>Repeat an automated Daily Quality Control after every 4 patients (8 scans) and record the results
Contact Jubilant DraxImage:
1-888-633-5343</td><td>The use of the RUBY-FILL® Rubidium Rb 82 Generator must be discontinued immediately.
Contact Jubilant DraxImage:
1-888-633-5343</td></tr>
<tr><td colspan="3">*USP limits: <0.02μCi of Sr-82/mCi of Rb-82; <0.2μCi of Sr-85/mCi of Rb-82</td></tr>
</table>
Table 3: Strontium Breakthrough Results

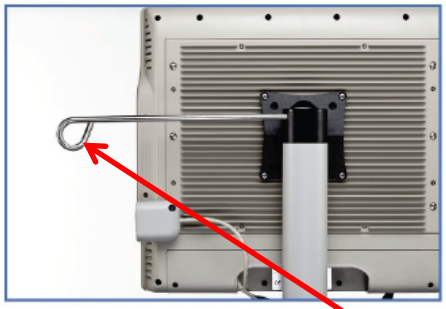
Id. at 44.
</td></tr>
</table>

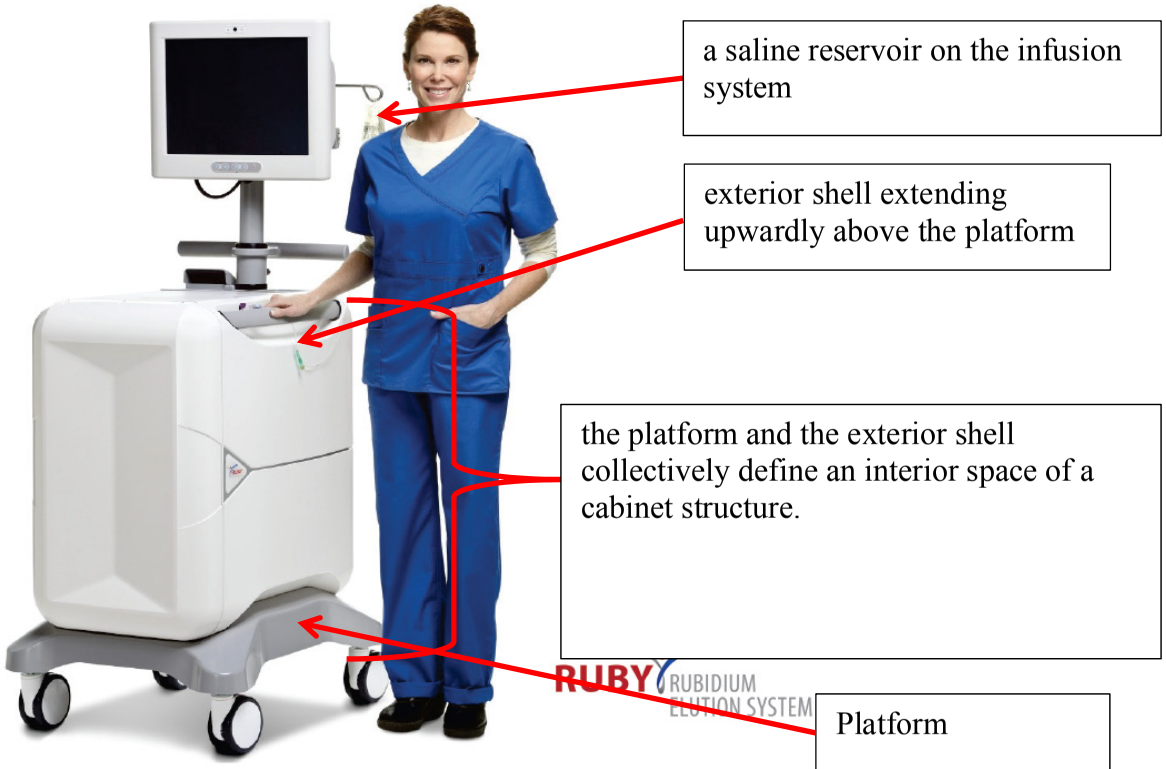
EXHIBIT 19

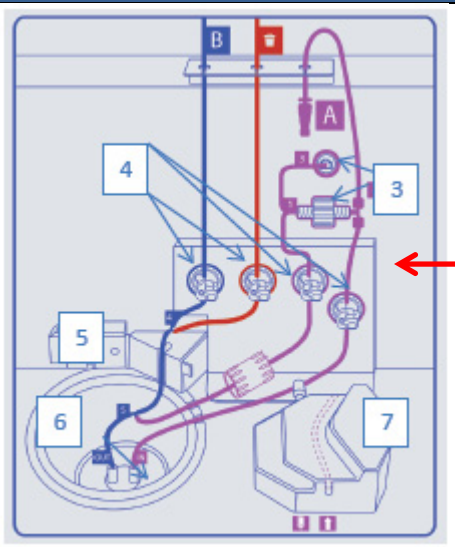
Exhibit No. 19

Bracco's infringement charts are exemplary in nature and not intended to be limiting. As explained herein, the Ruby-Fill Rubidium Elution System infringes the claims of the '870 patent literally or under the doctrine of equivalents. However, nothing in this chart is meant to preclude that any claim element is infringed literally or, alternatively, at a minimum under the doctrine of equivalents (even for any elements where doctrine of equivalents is not specifically identified). Bracco reserves all rights with respect to its infringement contentions that will be submitted during the Investigation and may depend on any claim construction Respondents newly raise.

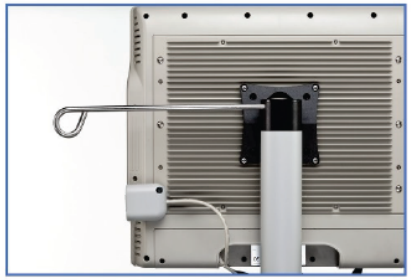
Claim 1 of the '870 Patent	Infringement Evidence
1. A method of using an infusion system on-board a cart to deliver a rubidium radioactive eluate comprising:	Jubilant has and will make, use, offer to sell, sell, and/or import into the United States an infusion system on-board a cart to deliver a rubidium radioactive eluate. Namely the Ruby-Fill System. In addition, as described herein, Jubilant's prescribing information and user manual instructs and encourages end-users to use an infusion system on-board a cart to deliver a rubidium radioactive eluate. The affirmative instructions in the prescribing information and user manual for Jubilant's Ruby-Fill system will induce end users to practice the method of claim 1 because the instructions in the prescribing information and/or user manual will result in the Ruby-Fill system being used in accordance with the steps of the claim. Jubilant's Ruby-Fill prescribing information and/or user manual encourages, recommends, and promotes use of the infringing method by end-users. Jubilant's knowledge of the '870 patent is evident from the filing of this complaint. Thus, Jubilant intends, and will cause, end-users to practice claim 1 of the '870 patent. Furthermore, there are no other substantial approved uses for Jubilant's Ruby-Fill system in the United States. Therefore, the manufacture and/or sale of Jubilant's Ruby-Fill system will contribute to and induce the infringement of claim 1 of the '870 patent by end users.

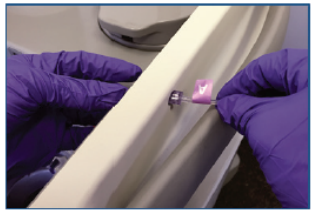
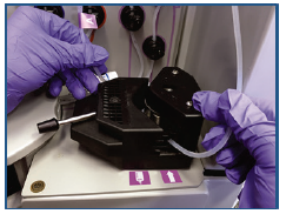
Claim 1 of the '870 Patent	Infringement Evidence
(a) installing a saline reservoir on the infusion system, wherein the infusion system comprises a platform and an exterior shell extending upwardly above the platform, and wherein the platform and the exterior shell collectively define an interior space of a cabinet structure;	The Ruby-Fill user manual instructs the installation of a saline reservoir on the infusion system. **3.4 SALINE BAGS, RUBY SALINE LINES, RUBY IV LINES** A bag of sterile 0.9% sodium chloride (additive free) injection, USP bag is installed by the user on the elution system to elute the generator. The saline bag hangs from a specially designed hook behind the computer screen (see Fig. 6, Saline Hook).  Figure 6, Saline Hook The RUBY SALINE LINE connects the saline bag to the RUBY SET. The RUBY SALINE LINE is installed by the user through the pump in the elution system and is aseptically connected to the "A" end of the RUBY SET via a luer-lock connection (RUBY SALINE LINE Installation, section 6.7). The RUBY SET terminates with a Luer-Lock fitting, "B" where the RUBY IV LINE is connected. An important feature of the RUBY IV LINE is an integrated 0.22 micron vented filter for increased patient safety (RUBY IV LINE Installation, section 6.8) *Id*. at 11. installing a saline reservoir on the infusion system Also, the Ruby-Fill system comprises a platform and an exterior shell extending upwardly above the platform, and wherein the platform and the exterior shell collectively define an interior space of a cabinet structure.

Claim 1 of the ’870 Patent	Infringement Evidence
	 *Id*. at 1;

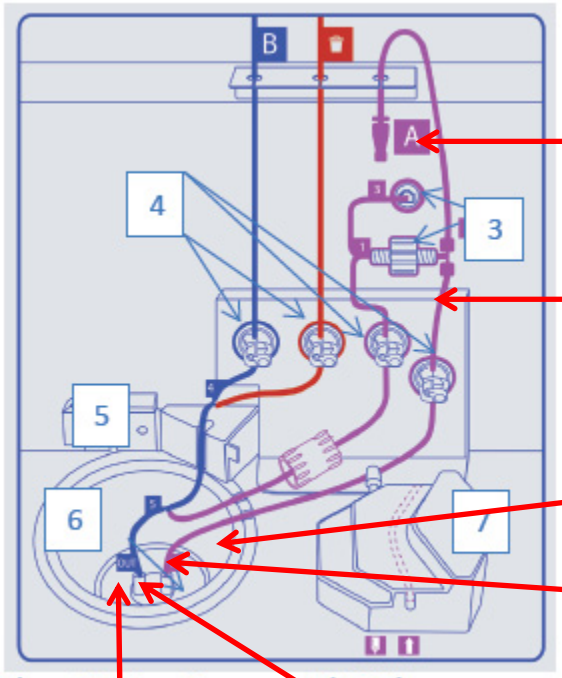
Claim 1 of the ’870 Patent	Infringement Evidence
	 Figure 2, System Components (#3–#7) an interior space of a cabinet structure *Id*. at 9;

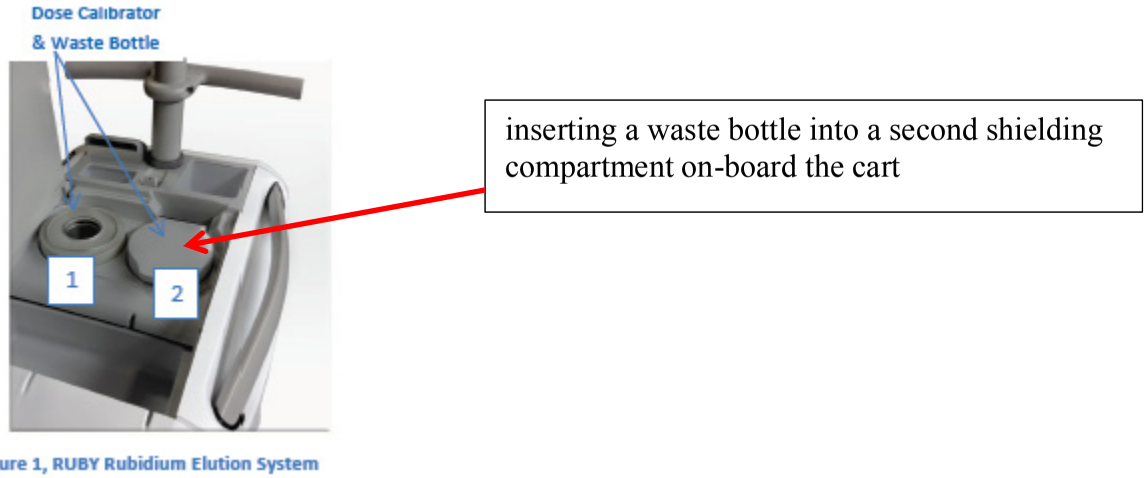
Claim 1 of the ’870 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1;

Claim 1 of the '870 Patent	Infringement Evidence
(b) placing the saline reservoir in fluid communication through a saline tubing line with an inlet tubing port of a strontium-rubidium radioisotope generator located in a first shielding compartment in the interior space of the cabinet structure, wherein the strontium-rubidium radioisotope generator further comprises an outlet tubing port configured to discharge the rubidium radioactive eluate, and wherein the first shielding compartment has a first opening facing vertically upwardly;	The Ruby-Fill user manual instructs placing the saline reservoir in fluid communication through a saline tubing line with an inlet tubing port of a strontium-rubidium radioisotope generator located in a first shielding compartment in the interior space of the cabinet structure, wherein the strontium-rubidium radioisotope generator further comprises an outlet tubing port configured to discharge the rubidium radioactive eluate, and wherein the first shielding compartment has a first opening facing vertically upwardly. **3.4 SALINE BAGS, RUBY SALINE LINES, RUBY IV LINES** A bag of sterile 0.9% sodium chloride (additive free) injection, USP bag is installed by the user on the elution system to elute the generator. The saline bag hangs from a specially designed hook behind the computer screen (see Fig. 6, Saline Hook).  Figure 6, Saline Hook The RUBY SALINE LINE connects the saline bag to the RUBY SET. The RUBY SALINE LINE is installed by the user through the pump in the elution system and is aseptically connected to the "A" end of the RUBY SET via a luer-lock connection (RUBY SALINE LINE Installation, section 6.7). The RUBY SET terminates with a Luer-Lock fitting, "B" where the RUBY IV LINE is connected. An important feature of the RUBY IV LINE is an integrated 0.22 micron vented filter for increased patient safety (RUBY IV LINE Installation, section 6.8) placing the saline reservoir in fluid communication through a saline tubing line with an inlet tubing port Exhibit No. 21 at 11;

Claim 1 of the '870 Patent	Infringement Evidence
	6.7 INSTALLING THE 0.9% SODIUM CHLORIDE (ADDITIVE FREE) INJECTION, USP (SALINE SUPPLY) & RUBY SALINE LINE A 0.9% sodium chloride (additive free) injection USP saline bag, RUBY SALINE LINE and RUBY IV LINE must be installed by the user to perform the Setup Validation in Daily Quality Control tab on the touchscreen monitor. 1. Visually inspect the RUBY SALINE LINE packaging for damage. Discard if damaged. 2. Using aseptic techniques, remove protective cap from saline bag and spike saline bag with the spike end of the RUBY SALINE LINE. 3. Ensure that the roller clamp is in the closed position on the RUBY SALINE LINE and hang the saline bag on the Saline hook. 4. Insert the RUBY SALINE LINE into the RUBY Rubidium Elution System via the keyhole on the right hand side of the system (see Fig. 39, RUBY SALINE LINE keyhole). 5. Open the pump by pulling lever **and** install the RUBY SALINE LINE into the pump (see Fig. 40, Installing RUBY SALINE LINE into Pump). Close the pump using the lever. 6. Using aseptic techniques, remove the protective cap of the RUBY SALINE LINE at point A and connect to the A portion of the RUBY SET (see Fig. 41, Attaching RUBY SALINE LINE to RUBY SET). 7. Open roller clamp on the RUBY SALINE LINE. 8. On the touch screen, select Pre-set Saline Volume (500mL or 1000ml) or Customized Saline Volume. The 0.9% USP saline bag must contain more than 50mL. 9. Change RUBY SALINE LINE with each new install of saline supply.  Figure 39, RUBY SALINE LINE Keyhole  Figure 40, Installing RUBY SALINE LINE into Pump *Id*. at 35;

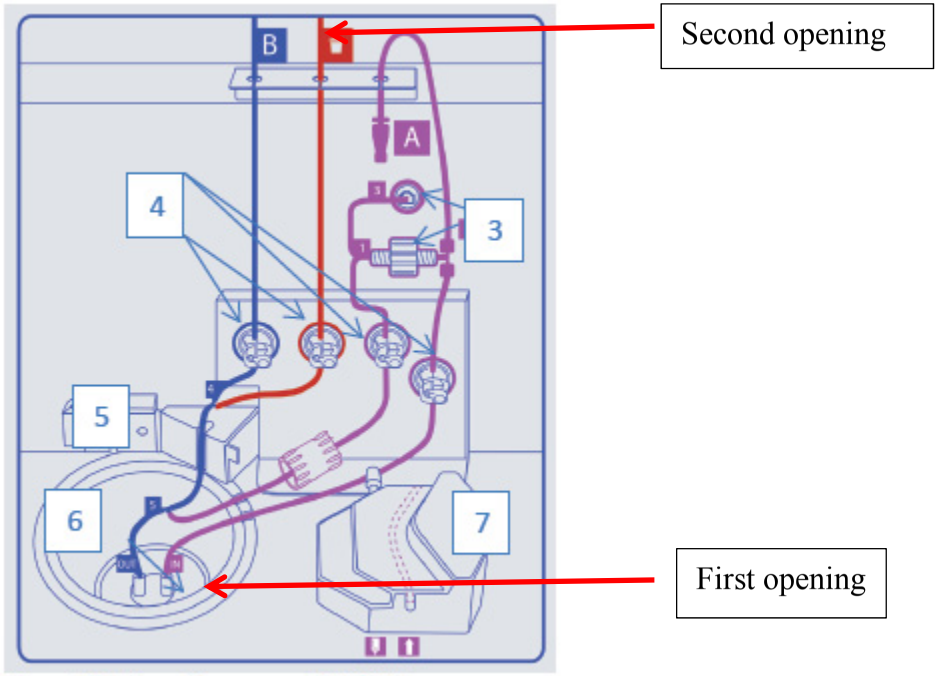
placing the saline reservoir in fluid communication through a saline tubing line with an inlet tubing port of a strontium-rubidium radioisotope generator

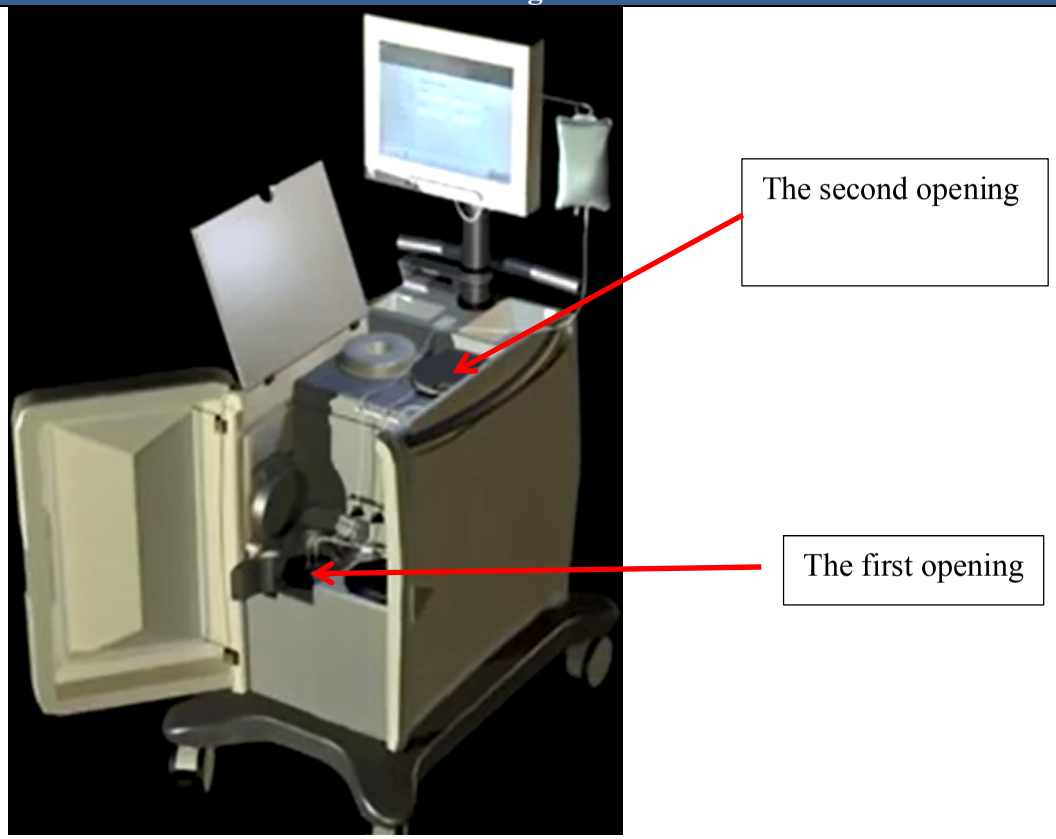
Claim 1 of the '870 Patent	Infringement Evidence
	 Figure 2, System Components (#3-#7) *Id.* at 9. to the saline reservoir a saline tubing line to inlet tubing port of strontium-rubidium radioisotope generator a first shielding compartment in interior space of the cabinet structure, wherein it has a first opening facing vertically upward inlet tubing port of a strontium-rubidium radioisotope generator outlet tubing port configured to discharge the rubidium radioactive eluate a strontium-rubidium radioisotope generator

Claim 1 of the '870 Patent	Infringement Evidence
(c) inserting a waste bottle into a second shielding compartment on-board the cart, wherein the second shielding compartment on-board the cart has a second opening facing vertically upwardly and being at a higher elevation than the first opening;	The Ruby-Fill user manual instructs inserting a waste bottle into a second shielding compartment on-board the cart, wherein the second shielding compartment on-board the cart has a second opening facing vertically upwardly and being at a higher elevation than the first opening.  Figure 1, RUBY Rubidium Elution System *Id.* at 9;

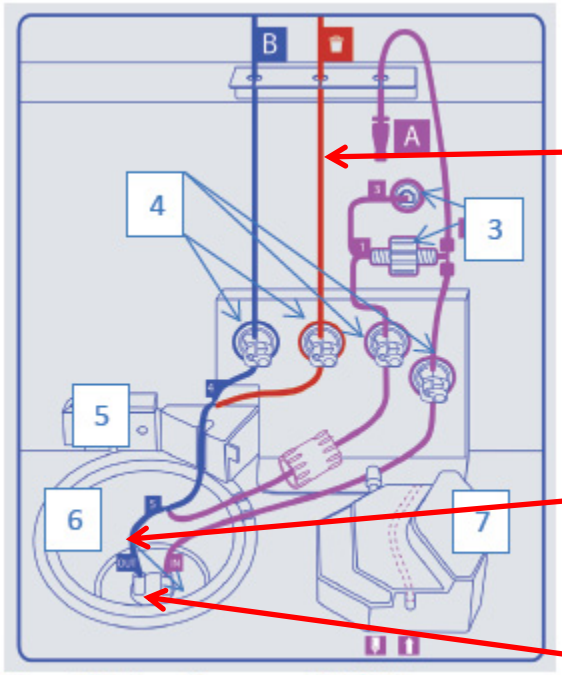
Claim 1 of the '870 Patent	Infringement Evidence
	3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).  Figure 7, Waste Bottle in Waste Well Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO). the second shielding compartment on-board the cart has a second opening facing vertically upwardly *Id*. at 12;

Claim 1 of the ’870 Patent	Infringement Evidence
	7.1 EMPTY WASTE CONTAINER To empty the liquid waste bottle, open the shielded lid and disconnect the tube from the bottle and discard the solution according to local regulations. Reinstall the waste bottle; making sure the tube is correctly installed to avoid leaks into the well. Close the lid and press **Next** on the Empty Waste Screen (see Fig.44, Empty Waste Screen). Discard the waste solution according to local regulations and procedures for radioactive waste. Failure to empty the waste daily could cause the waste bottle (1L fluid limit) to overflow into the waste well. If this occurs, remove the liner and clean waste well per site-specific procedures.  Figure 44, Empty Waste Screen *See also id.* at 38;

Claim 1 of the ’870 Patent	Infringement Evidence
	 Figure 2, System Components (#3-#7) *Id*. at 9 (second opening being at a higher elevation than the first opening);

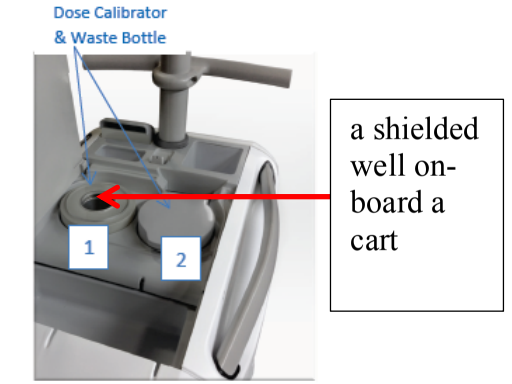
Claim 1 of the ’870 Patent	Infringement Evidence
	 *See also* Physical Exhibit No. 1 (second opening being at a higher elevation than the first opening). .

Claim 1 of the '870 Patent	Infringement Evidence
(d) placing the waste bottle in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator through an eluate tubing line, wherein a computer on-board the cart is configured to control the fluid communication between the waste bottle and the outlet tubing port, and wherein the computer has a touch screen display mounted on a vertical post with a top end extending above the cabinet structure;	The Ruby-Fill user manual instructs placing the waste bottle in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator through an eluate tubing line, wherein a computer on-board the cart is configured to control the fluid communication between the waste bottle and the outlet tubing port, and wherein the computer has a touch screen display mounted on a vertical post with a top end extending above the cabinet structure. **6.5 INSTALLING THE RUBY SET** 11. Remove the protective cap and attach the Waste portion of tubing (next to the Red Trash Icon) to the Waste Bottle. Exhibit No. 20 at 31-32;  Figure 7, Waste Bottle in Waste Well placing the waste bottle in fluid communication with the outlet tubing port *Id*. at 12;

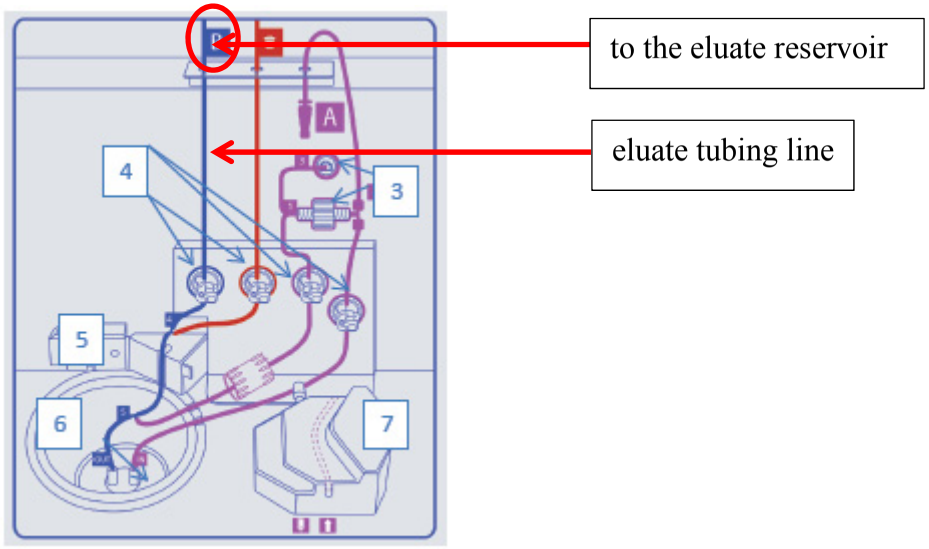
Claim 1 of the ’870 Patent	Infringement Evidence
	 Figure 2, System Components (#3-#7) *Id.* at 9;

Claim 1 of the ’870 Patent	Infringement Evidence
	2.2 SYSTEM DESCRIPTION The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions. The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message. *Id*. at 8 a computer on-board the cart is configured to control the fluid communication between the waste bottle and the outlet tubing port, and wherein the computer has a touch screen display mounted on a vertical post with a top end extending above the cabinet structure

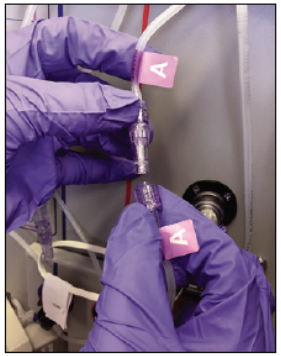
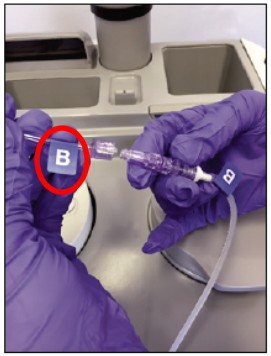
Claim 1 of the ’870 Patent	Infringement Evidence
	 *Id*. at 1.

Claim 1 of the '870 Patent	Infringement Evidence
(e) inserting an eluate reservoir in a shielded well on-board the cart;	The Ruby-Fill user manual instructs inserting an eluate reservoir in a shielded well on-board the cart. **2.3 MAIN SYSTEM COMPONENTS** The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components): 1. Dose Calibrator 2. Waste Bottle 3. Pressure Transducer Holder and Connector 4. Pinch valves (four) 5. Photo Multiplier Tube (PMT) 6. Generator Well 7. Peristaltic Pump 8. Touch Screen Computer User Interface (not shown) 9. Removable Storage Compartment (not shown)  Figure 1, RUBY Rubidium Elution System *Id*. at 9;

Claim 1 of the ’870 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber. 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *See, e.g., id.* at 42.

Claim 1 of the '870 Patent	Infringement Evidence
(f) placing the eluate reservoir in fluid communication with the eluate tubing line, wherein the computer is further configured to control the fluid communication between the eluate reservoir and the eluate tubing line;	The Ruby-Fill user manual instructs placing the eluate reservoir in fluid communication with the eluate tubing line, wherein the computer is further configured to control the fluid communication between the eluate reservoir and the eluate tubing line.  Figure 2, System Components (#3–#7) *Id*. at 9;

Claim 1 of the ’870 Patent	Infringement Evidence
	The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *See, e.g., id.* at 42 (placing the eluate reservoir in fluid communication with the eluate tubing line);

Claim 1 of the ’870 Patent	Infringement Evidence
	6.8 INSTALLING THE RUBY IV LINE 1. Visually inspect the RUBY IV LINE packaging for damage. Discard if damaged. 2. Using aseptic techniques, remove cap from B end of RUBY IV LINE and connect to B end of RUBY SET (see Fig. 42, Installing RUBY IV LINE). 3. A new RUBY IV LINE must be used for each patient. 4. The patient end of the RUBY IV Line (yellow sticker with patient icon) is connected to the patient. 5. Between Rubidium-82 Chloride injections (rest & stress) and if the RUBY IV LINE is disconnected from the patient, engage the clamp to close the line. 6. After each patient, and at the end of the day, remove and discard used RUBY IV LINE from the RUBY SET and discard according to local procedures for potentially biohazardous materials.  Figure 41, Saline Line to RUBY SET  Figure 42, Installing RUBY IV Line *Id*. at 36;

Claim 1 of the ’870 Patent	Infringement Evidence
	2.2 SYSTEM DESCRIPTION The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions. The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions. The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message. the computer is further configured to control the fluid communication between the eluate reservoir and the eluate tubing line *Id*. at 8.

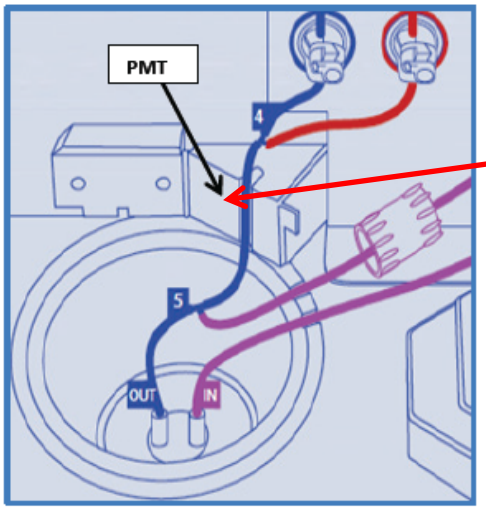
Claim 1 of the '870 Patent	Infringement Evidence
(g) pumping a sample of the rubidium radioactive eluate into the eluate reservoir in the shielded well on-board the cart;	The Ruby-Fill user manual instructs pumping a sample of the rubidium radioactive eluate into the eluate reservoir in the shielded well on-board the cart. The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber. 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id.* at 42.
(h) measuring a radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line with a radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line;	The Ruby-Fill user manual instructs measuring a radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line with a radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line.

Claim 1 of the '870 Patent	Infringement Evidence

System Error Message	Message Meaning	How to Troubleshoot
Radioactivity Counter Overlight	The radioactivity counter is exposed to light	▪ Verify that the radioactivity counter cover is closed.
Radioactivity Counter Failure	Error detected from the radioactivity counter	▪ Verify that the radioactivity counter cover is closed. ▪ Restart the system.
Radioactivity Counter Disconnected	Communication failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.
Radioactivity Counter Error	System detected a failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.
Radioactivity Counter Initialization Error	System detected a failure with the radioactivity counter	▪ Verify that the acquisition card cable is connected to the computer. ▪ Restart the system.

Id. at 59;

12. Insert line section between #4 and #5 into groove of the PMT, ensuring PMT door may be closed properly after tube placement (See Fig. 33, Installation of PMT portion of RUBY SET).



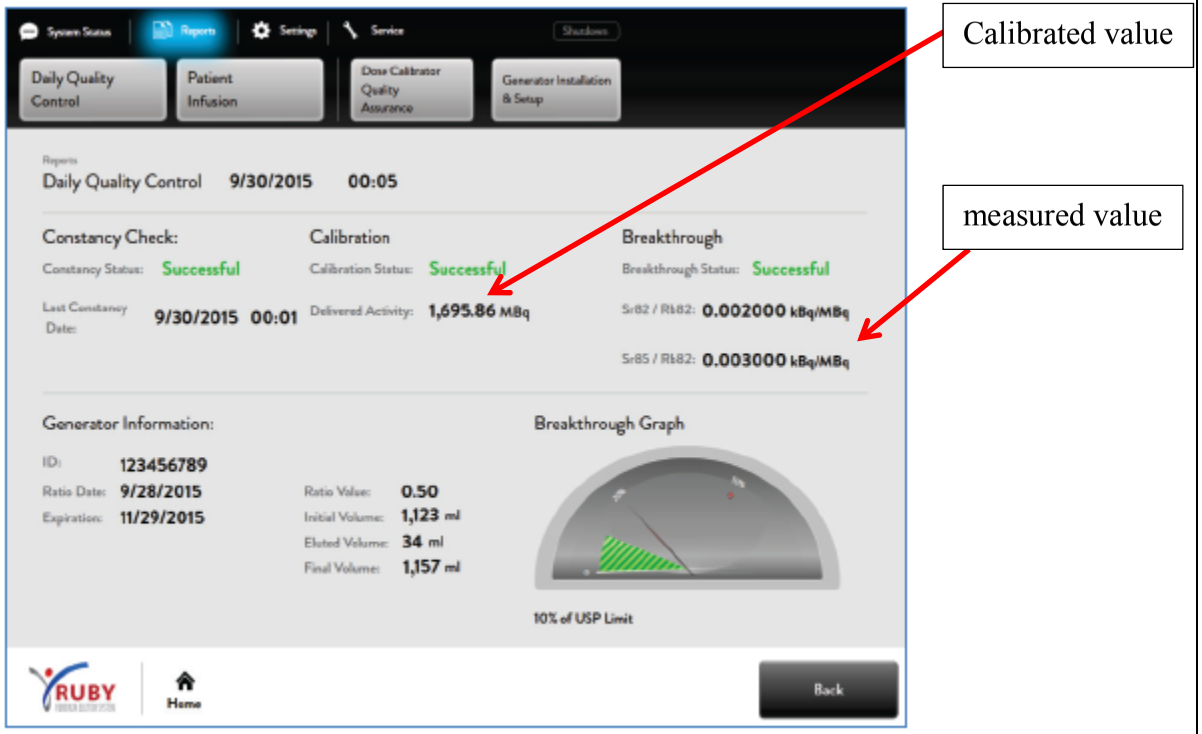
a radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line

Figure 33, Installation of PMT portion of RUBY SET

Id. at 32.

Claim 1 of the '870 Patent	Infringement Evidence
(i) measuring a calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart;	The Ruby-Fill user manual instructs measuring a calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart. The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id.* at 42.

Claim 1 of the '870 Patent	Infringement Evidence
(j) comparing the radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line measured by the radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line with the calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart; and	The Ruby-Fill user manual instructs comparing the radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line measured by the radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line with the calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart. The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id.* at 42; **8. PATIENT INFUSIONS** In the event of hardware failure or significant discrepancy between measured and expected values, the software automatically terminates the elution and displays the appropriate error message. *Id.* at 46, 49;

Claim 1 of the ’870 Patent	Infringement Evidence
	 **Figure 59, Daily Quality Control Report Screen** *Id*. at 51.

Claim 1 of the '870 Patent	Infringement Evidence
(k) determining a strontium breakthrough test result on the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, wherein the computer of the infusion system is further configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.	The Ruby-Fill user manual instructs determining a strontium breakthrough test result on the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, wherein the computer of the infusion system is further configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit. The calibration process runs a measured amount (35mL) of saline through the Generator at a flow rate of 20 mL/min to deliver a calibrated sample. This calibrated sample is collected in a vial in the dose calibrator and measured to determine the activity. This activity will be used by the system to determine the activity available at this point in the life of the Generator and to measure the activity delivered in patient infusions. The breakthrough test uses the sample produced during the calibration process. This portion of the Daily Quality Control takes 30 minutes, during which the Rb-82 decays completely, and the system assays the calibration sample and measures the amount of strontium-82 and strontium-85 present in the sample. This information is saved in the calibration report (refer to section 8.1, Reports). Follow these steps before initiating Start for the Flush, Calibration and Breakthourgh. 1. Obtain a 50 ml sealed glass vial (with rubber stopper) 2. Aseptically install a RUBY IV LINE on the B needleless injection port of the RUBY SET 3. Aseptically install a sterile needle (20G) on the end of the RUBY IV LINE and insert into rubber stopper of glass vial 4. Insert a sterile vent needle (20G) into rubber stopper of glass vial 5. Place the vial into dose calibrator dipper and lower into the dose calibrator chamber 6. Press Start to begin the 50-minute procedure (see Fig. 49, Flush, Calibration, and Breakthrough Screen). *Id*. at 42;

Claim 1 of the ’870 Patent	Infringement Evidence

Figure 49, Flush, Calibration, and Breakthrough Screen

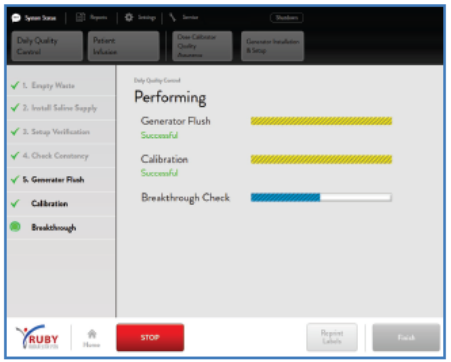


Figure 50, Performing Daily Quality Control (Flush and Calibration are completed and the Breakthrough Check is in progress)

The yellow progress bar indicates that a radioactive procedure is in progress and that radioactive solution is flowing through unshielded tubes. The user should remain at a safe distance from the elution system.

When the breakthrough check is complete, a label with the daily QC values automatically prints as configured in the settings. The user can either press Reprint Labels or press **Finish**.

When the user selects **Finish**, the Ready for Patient Infusion Screen appears (see Fig. 51, Ready for Patient Infusion Screen). This screen displays important information about the state of the elution system at a glance. The most important information displayed on this screen is:

- Breakthrough: Indicated as a percentage of the USP limit* (see Table 3), this field indicates the level of impurities calculated in the Daily Quality Control.
- Breakthrough History: The graph tracks the breakthrough levels for each day of use of the installed generator.
- Below the yellow line (<20% of USP limit*, see Table 3), the system can be used without any restriction on the number of infusions per Quality Control.
- An alert limit is reached when the reading is above the yellow line (≥ 20%) and below the red line (<50% of the USP limit*, see Table 3). Alert limits may be triggered by the following:
    - 20 L of saline eluted through the Generator.
    - or an eluate Sr-82 level of ≥0.004 µCi/mCi Rb-82. and ≤ 0.01 µCi/mCi Rb-82.
    - or an eluate Sr-85 level of ≥0.04 µCi/mCi and ≤ 0.1 µCi/mCi Rb-82.

Id. at 42-43;

Claim 1 of the '870 Patent	Infringement Evidence

System Error Message	Message Meaning	How to Troubleshoot
Sr Breakthrough Too High	The breakthrough limit level is reached. Patient infusions not allowed.	▪ Verify that the generator is not expired. ▪ Verify background activity fluctuations. ▪ Repeat radioactivity calibration and breakthrough check. ▪ Install a new generator.

Id. at 59;

The system can be used with four (4) patients before a Quality Control procedure must be performed if the breakthrough reaches an alert limit. If the user repeats the flush, the system counts this as a patient infusion.

- ≥ 50% of the USP limit* (see Table 3), the system does not allow the user to perform a patient infusion.
- Refer to Table 3 below for instructions to follow on Strontium Breakthrough results.

PASS < 20% of USP limits* (Green)	ALERT ≥ 20% and <50% of USP limits* OR 20L volume limit (Yellow)	FAIL ≥ 50% of USP limits* OR 30L volume limit (Red)
Breakthrough level is low.	Breakthrough level is increased.	Breakthrough level is approaching the allowable limit.
The Daily Quality Procedure (automated breakthrough test) is valid for a 24 hour period.	The Daily Quality Procedure (automated breakthrough test) is valid for 4 patients only.	The Daily Quality Control (automated breakthrough test) does not allow a sufficient margin of safety to continue the elutions (scans).
Proceed with use	Repeat an automated Daily Quality Control after every 4 patients (8 scans) and record the results Contact Jubilant DraxImage: 1-888-633-5343	The use of the RUBY-FILL® Rubidium Rb 82 Generator must be discontinued immediately. Contact Jubilant DraxImage: 1-888-633-5343
*USP limits: <0.02μCi of Sr-82/mCi of Rb-82; <0.2μCi of Sr-85/mCi of Rb-82		

Table 3: Strontium Breakthrough Results

Id. at 44.

EXHIBIT 20

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202153Orig1s000

Trade Name:	**RUBY-FILL**
Generic or Proper Name:	**rubidium Rb 82 generator**
Sponsor:	**Jubilant DraxImage, Inc.**
Approval Date:	**September 30, 2016**
Indication:	**for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
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REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology/Virology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-153

NDA APPROVAL

Jubilant DraxImage, Inc.
Attention: Aziz R. Nuritdinov
Regulatory Associate, Regulatory
Strategy, Consulting & Submissions
Inc. Research, LLC, US Agent
441 Vine Street, Suite 400
Cincinnati, OH 45202

Dear Mr. Nuritdinov:

Please refer to your New Drug Application (NDA) dated June 18, 2010, received June 30, 2010, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruby-Fill® (Rubidium Rb-82 Generator 85-115mCi).

We acknowledge receipt of your amendment dated December 28, 2015, which constituted a complete response to our December 18, 2014, action letter.

We further acknowledge receipt of your major amendment dated June 11, 2016, which extended the goal date by three months.

This new drug application provides for the use of Ruby-Fill® (Rubidium Rb-82 Generator 85-115mCi) for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202153**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Frank Lutterodt, Senior Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Product
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CC: Magali Lurquin
Associate Director, Regulatory Affairs
Jubilant DraxImage Inc.
16751 Trans-Canada Highway
Kirlkland, Quebec, Canada, H9H 4J4

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

LIBERO L MARZELLA
09/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-153

COMPLETE RESPONSE

INC Research LLC
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Attention: Greg Hockel, Ph.D.
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

Dear Dr. Hockel:

Please refer to your New Drug Application (NDA) dated June 18, 2010, received June 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We acknowledge receipt of your amendments dated May 18, 20, August 29, December 6, 20, 2011, October 25 2012, January 17, February 14, May 21, August 3, September 19, 23, 2013, March 11, 25, and May 12, 2014.

We have completed our review of this application, as amended, and as stated in our December 12, and December 17, 2014 teleconference with your firm, have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The reports of the human factor studies titled: "Ruby Rubidium Elution System Summative Usability Validation Report" and "Ruby Rb-82 Elution System Usability Risk Analysis" are materially incomplete. We request that you provide the following:

    a. study protocols;
    b. data (in the same format as the Hartford site) from subjects at the Brigham and Women's and Cardiac Imaging Associates sites participating in the study;
    c. training or user manual that was the basis of training for the validation report;
    d. mitigation strategies (such as responses to computer input errors) that have been instituted and thereport of any additional study performed to confirm the effect of these strategies.

2. A training/re-training program and training packages need to be finalized prior to marketing. We request that you provide:

a. an initial and on-going training program and a methodology to evaluate its effectiveness;

b. a final version of an Instructions for Use (IFU) document which is structured with a table of contents, index, page numbering and a section on responding to serious patient emergencies involving Ruby-Fill administration. Clarify whether this IFU is intended to also serve as a training manual or if a separate training manual will be provided.

PRODUCT QUALITY

3. The post-approval (b) (4) testing protocol proposed is not sufficient (b) (4) We request that you revise the testing protocol as follows:

   a. (b) (4)

   b. (b) (4)

   c. (b) (4)

4. Regarding the Ruby Elution SystemInstructions for Use (IFU) document:

   a. Clarify the description and sources of the listed supplies, and whether they are supplied by Jubilant DraxImage with the Elution System;

   b. specify the recommended (b) (4) (see page 10, supplies);

   c. describe and label (b) (4) as they are essential to the operation of the Elution System (page A|1– system consumables).

System Description and Requirements Specifications

5. The design implementation is not described technically in the submission. Some of the documents provide insight into the system requirements, such as the user manual, package insert and pharmaceutical development documentation (eCTD Module III – 3.2.P.2). However, it is not clear how these requirements have been implemented into

system specifications and it is not clear that the complete set of requirements has been documented. Please provide the following additional information:

a. Documentation describing system requirements and demonstrating the implementation of the requirements into the design.
b. A process model and a functional diagram depicting the functions of the system.
    i. The process model should describe automated controls, the controlled processes, and human interaction.

    ii. The functional diagram should identify functional components of the system and describe their interactions to achieve the intended use.

c. Identify and describe [redacted] (b) (4) other disposable components

Hazards Analysis and Safety Requirements

6. We have completed our review of the documentation submitted in support of the Ruby Elution System. During our review we evaluated the documentation to determine if hazards associated with the use of this device are adequately addressed. A document titled "Draximage Rb-82 Version 3 Hazard Analysis", dated May 2011, was provided for review. This document does not provide the detailed analysis of hazards, hazard causes, and safety requirements implemented to assure the safety the Ruby Elution System. To assure the safety of the delivery system, we need to review documentation demonstrating that potential hazards to the patient and user have been reasonably mitigated. We have identified some of the system hazards that need to be addressed, which include:

    a. Unintended radiation exposure (patient and healthcare provider)
    b. Rubidium delivery error (overdose or underdose)
    c. Volume overload
    d. Embolus (air or particulate)
    e. Biological safety (biocompatibility, sterility, infectious agent cross-contamination between patients). It is noted that the final specifications for the delivery system [redacted] (b) (4) and accessory components have not been submitted and there is no information in the submission to demonstrate that biocompatibility, sterility, shelf life of disposables, and infectious agent cross-contaminations of patients have been adequately addressed.

    Your own analyses may have identified additional system hazards. Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of the system hazards we have identified from our review and any additional system hazards you may have identified. For each identified cause, provide the following:

    a. Describe the control method for each identified cause.

    b. For each cause, provide an explanation justifying the adequacy of the control to mitigate the respective system hazard.

c. Provide evidence verifying the control method adequately addresses the respective cause / hazard.

System Performance and Reliability

7. The system includes three delivery modes: [redacted] (b) (4) Provide the following information regarding these delivery modes:
   a. Identify the requirements and specifications for each delivery mode.
   b. Verify that the design of each delivery mode does not permit the system to exceed dose or volume limits.
   c. Provide evidence verifying and validating the software algorithms used to achieve each delivery mode are correctly implemented into the system.

8. The system contains several functional components necessary to achieve the system's intended use. These include [redacted] (b) (4) Provide data demonstrating that the implementation of these components achieve the specified performance and reliability specifications to assure the safe and effective use of the system.

9. [redacted] (b) (4) The submission does not provide information regarding possible degradation of system components over the 60 day use period. Possible causes of safety and effectiveness degradation include the following:

   a. Exposure to radiological activity.
   b. [redacted] (b) (4)
   c. [redacted] (b) (4)
   d. Microbiological growth.

   Provide data demonstrating that 60 day use of the components will not degrade the safety and effectiveness of the system to an unacceptable level.

10. [redacted] (b) (4) Describe the mechanism implemented [redacted] (b) (4) and present evidence demonstrating their effectiveness. As part of this assessment, consider scenarios [redacted] (b) (4)

11. The manual instructs users [redacted] (b) (4) Provide a risk assessment addressing this potential hazard.

12. The manual states that the system is [redacted] (b) (4) Please provide documentation to support this claim.

13. In addition to being a potential source of embolus, the submission notes that air in the infusion system can result in dose errors. The submission does not clearly address how you have assured that air will not be present within the infusion system, either as a dose error hazard or air embolus hazard. Please provide a risk assessment for these two hazards, identify appropriate controls and provide evidence to support the conclusions.

Software

14. The submission does not include documentation demonstrating that the software has been adequately verified and validated. Provide the following information:

    a. A software description providing a summary overview of the features and software operating environment.

    b. A device hazard analysis identifiying software hazards, including severity assessment and mitigations.

    c. The complete software requirements specification document.

    d. A detailed depiction of functional units and software modules.

    e. A traceability analysis demonstrating traceability among all requirements, specifications, identified hazards and mitigations, and verification and validation testing.

    f. A summary software life cycle development plan, which must include an annotated list of control documents generated during the development process, the configuration management plan and the maintenance plan.

    g. A description of verification and validation activities at the unit, integration, and system level. Unit, integration and system level test protocols must be provided and must include pass/fail criteria, test report, test summary and test results.

    h. The revision history log, including release version number and date.

    i. A list of unresolved anomalies. For each unresolved anomaly, provide the following information:

        i. A description of the anomaly from a symptom point of view and how it is manifested.
        ii. The location in the code where the anomaly occurs.
        iii. A description of how to fix the anomalous code.

iv. A search of the software source code for other possible instances of the anomaly. For example, if the problem was an off-by-one error in an array, provide evidence that all arrays were checked for off-by-one errors.
v. Provide evidence that a coupling analysis was performed to identify all parts of the software that accessed the anomalous code and that no problems would arise because of accessing this anomalous code.
vi. Provide evidence that the anomalies are corrected, or provide an explanation for why the anomaly is not likely to result in harm if it occurs.
vii. Provide a time-frame for resolving any unresolved anomalies determined to be low risk.

j. Provide a static analysis of all software in your system. The information provided should describe the static analysis tools used to evaluate your software, the criteria applied for correcting or not correcting coding errors/warnings, evaluation of the static analysis results, and conclusions.

15. If the system includes off-the-shelf (OTS) software, you should provide the following information:

a. An analysis of hazards associated with the implementation of OTS software in the Ruby Elution System. The OTS software hazards analysis must include:

b. A list of all potential hazards identified.

c. The estimated severity of each identified hazard.

d. A list of all potential causes of each identified hazard.

e. The steps taken to mitigate each hazard.

f. Evidence that the product development methodologies used by the OTS Software developer are appropriate and sufficient for the intended use of the OTS Software within the Ruby Elution System. This should include an audit of the OTS Software developer's design and development methodologies used in the construction of the OTS Software. This audit should thoroughly assess the development and qualification documentation generated for the OTS Software.

g. Evidence that the procedures and results of the verification and validation activities performed for the OTS Software are appropriate and sufficient for the safety and effectiveness requirements of the Ruby Elution System. Verification and validation activities include not only those performed by the OTS Software developer, but also include those performed by the Jubilant Draximage when qualifying the OTS Software for its use in the Ruby Elution System.

h. Demonstrate the existence of appropriate mechanisms for assuring the continued maintenance and support of the OTS Software should the original OTS Software developer terminate their support.

Electrical Safety and Electromagnetic Compatibility

16. Provide information demonstrating compliance with relevant electrical safety and electromagnetic compatibility requirements of IEC 60601-1 (1988): Medical electrical equipment – Part 1: General requirements for safety, including Amendment 1 (1991) and Amendment 2 (1995) for Type B equipment and IEC 60601-1 Collateral Standard: Safety requirements for medical electrical systems and IEC 60601-1-2 (2001): Medical Electrical Equipment, Part 1: General Requirements for Safety, 2. Collateral Standard: Electromagnetic Compatibility - Requirements and Tests.

Biocompatibility and Infection Control

17. All drug path devices are required to be sterile. The submission does not contain any data demonstrating assurance and maintenance of sterility for the disposable components of the Ruby Elution System. Provide the following information:
    a. A copy of the package labeling for each disposable component indicating the contents are sterile.
    b. Description of the sterilization method.
    c. If using radiation sterilization methods, identify the dose.
    d. If using ethylene oxide gas sterilization, identify the acceptable limits for sterilant residuals remaining on the device.
    e. A description of the Validation Method for the sterilization cycle.
    f. Sterility assurance level (SAL).
    g. Provide pyrogen testing and acceptable endpoints.
    h. A description of the (b) (4) packaging.
    i. Provide documentation supporting the shelf life of the disposable components.

18. Identify the finished products that comprise the drug pathway and provide data demonstrating the biocompatibility of these products. Included in this, you should provide a chemical and particulate characterization on the final, finished, fluid contacting drug pathway components demonstrating that risk of harm from device-related residues is reasonably low. All testing should be conducted on finished, sterile product. For the assessment, we recommend the following:

    a. For device-related chemical residual characterization, the Agency recommends performing a leachables and extractables (L&E) study.

    b. For device-related particulate evaluation, you should follow current USP <788> Particulate Matter in Injections. FDA considers USP <788> to be limited to evaluation of micron particles.

    c. Device-related residual characterization alone may not provide appropriate information for risk of harm from device-related residues. The Agency recommends a comprehensive risk assessment of the device-related residuals

based on route of exposure, toxicokinetics and toxicodynamics, and allowable limits in the intended population proposed for the new device.

19. We are concerned about the risk of disease transmission occurring from cross-contamination in devices [redacted] (b) (4) such as yours. The information in your submission does not provide adequate assurance that the risk of cross-contamination has been adequately mitigated by the design of your system and that the risk outweighed by the benefit [redacted] (b) (4) Provide the following information:

    a. Demonstrate that the risk of cross-contamination has been adequately mitigated, which should include suitable challenge testing to support your conclusions.

    b. Provide information supporting the conclusion that cross-contamination risks are outweighed by the benefit [redacted] (b) (4)

PRESCRIBING INFORMATION

Complete labeling revisions will be provided at the time of an Approval action. However, at the time we have the following suggested revision:
Section 2.5 Elution testing protocol and Boxed Warning: Repeat testing for Strontium breakthrough after every 4 patients may lead to variability since elution volumes may differ with individual patients. Provide an elution volume in mL between which repeat testing for Strontium breakthrough should take place.

20. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

    - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
    - Regulations and related guidance documents
    - A sample tool illustrating the format for Highlights and Contents, and
    - The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

    Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

21. Please refer to correspondence dated, DATE which addresses the proposed proprietary name, PROPRIETARY NAME. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

LIBERO L MARZELLA
12/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RUBY-FILL safely and effectively. See full prescribing information for RUBY-FILL.

RUBY-FILL (rubidium Rb 82 generator)
To produce rubidium Rb 82 chloride injection, for intravenous use
Initial U.S. Approval: 1989

WARNING: UNINTENDED STRONTIUM 82 (Sr 82) AND STRONTIUM 85 (Sr 85) RADIATION EXPOSURE
Please see full prescribing information for complete boxed warning
- **Unintended radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed specific limits. (5.1)**
- **Perform generator eluate tests:**
  1) Determine Rb 82, Sr 82, Sr 85 levels in the eluate:
    - **Once daily, prior to any drug administration, and**
    - **With additional daily tests after detection of an Alert Limit. (2.6)**
  2) Stop use of the generator at its Expiration Limit. (2.7)

----------INDICATIONS AND USAGE----------
RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease. (1)

----------DOSAGE AND ADMINISTRATION----------
Use RUBY-FILL with a specific Elution System. (2.4)
- The recommended weight-based dose of rubidium Rb 82 is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg]. (2.2)
- Do not exceed a single dose of 2220 MBq (60 mCi) per rest or stress component of a procedure. (2.2)
- Administer the single dose at a rate of 15 - 30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 mL. (2.2)
- Use the lowest dose necessary to obtain adequate cardiac visualization and individualize the dose depending on multiple factors, including, patient weight, imaging equipment and acquisition type used to perform the procedure. (2.2)
- Start imaging acquisition 60-90 seconds after completion of the infusion; if a longer circulation time is anticipated, wait for 120 seconds. Acquisition may be started immediately post-injection if dynamic imaging l is needed. Image acquisition is typically 3-7 minutes long. (2 3)
- To obtain rest and stress images, wait 10 minutes after completion of the rest image acquisition then administer the pharmacologic stress agent in accordance with its prescribing information. After administration of the pharmacologic stress agent, infuse the second dose of Rb 82, at the time interval according to the prescribing information of the pharmacological stress agent and complete the stress image acquisition. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
RUBY-FILL consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145 - 4255 MBq (85 - 115 mCi) Sr 82 at calibration time. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Unintended radiation exposure occurs when Sr 82 and Sr 85 levels in rubidium Rb 82 chloride injection exceed specified generator eluate limits. (5.1)
- Pharmacologic induction of cardiovascular stress: May be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform testing only in setting where cardiac resuscitation equipment and trained staff are readily available. (5.2)

----------ADVERSE REACTIONS----------
To report SUSPECTED ADVERSE REACTIONS, contact Jubilant DRAXIMAGE Inc. at 1-888-633-5343 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Do not resume breastfeeding until at least one hour after completion of RUBY-FILL infusion. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: UNINTENDED STRONTIUM 82 (Sr 82) AND STRONTIUM 85 (Sr 85) RADIATION EXPOSURE

Unintended radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed specified limits *[see Warnings and Precautions (5.1)]*.

Perform generator eluate tests:

1) The system automatically generates a record and saves the data for each generator eluate volume, including flushing and test volumes. Total cumulative eluate volumes are also recorded and saved for the life of the generator *[see Dosage and Administration (2.5)]*.

2) Determine Rb 82, Sr 82, Sr 85 in the generator eluate:

- **Once a day, prior to any drug administration, and**
- **At additional daily tests after detection of an Alert Limit. Alert Limits are:**
  - **20 L for the generator's cumulative eluate volume, or**
  - **An eluate Sr 82 level of 0.004 μCi/ mCi (kBq/MBq) Rb 82, or**
  - **An eluate Sr 85 level of 0.04 μCi/ mCi (kBq/MBq) Rb 82.**
- **Perform additional daily tests every 4 patients after detection of an alert limit *[see Dosage and Administration (2.6)]*.**

3) Stop use of a generator at any of the following Expiration Limits. Expiry Limits are:

- **30 L for the generator's cumulative eluate volume, or**
- **Expiration date of the generator (60 days post-manufacturing)**
- **An eluate Sr 82 level of 0.01 μCi /mCi (kBq/MBq) Rb 82, or**
- **An eluate Sr 85 level of 0.1 μCi /mCi (kBq/MBq) Rb 82 *[see Dosage and Administration (2.7)]*.**

1 INDICATIONS AND USAGE

RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

Rubidium Rb 82 is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration *[see Warnings and Precautions (5.3)]*.

- Use waterproof gloves and effective shielding when handling rubidium Rb 82 chloride injection and the RUBY Rubidium Elution System.
- Use aseptic techniques in all drug handling.
- Visually inspect the drug for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer eluate from the generator if there is any evidence of foreign matter.

2.2 Recommended Dose and Administration Instructions

- The recommended weight-based dose of rubidium Rb 82 chloride to be administered per rest or stress component of a PET myocardial perfusion imaging (MPI) procedure is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg].
- Do not exceed a single dose of 2220 MBq (60 mCi).
- Use the lowest dose necessary to obtain adequate cardiac visualization and individualize the weight-based dose depending on multiple factors, including, patient weight, imaging equipment and acquisition type used to perform the procedure. For example, 3D imaging acquisition may require doses at the lower end of the recommended range compared to 2D imaging.
- Administer the single dose at a rate of 15 - 30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 mL.
- Instruct patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.
- The maximum available activity (delivery limit) will decrease as the generator ages *[see Dosage and Administration (2.8)]*.

2.3 Image Acquisition Guidelines

For Rest Imaging:

- Administer a single ("rest") rubidium Rb 82 chloride dose;
- Start imaging 60-90 seconds after completion of the infusion of the rest dose and acquire images for 3-7 minutes.

For Stress Imaging:

- Begin the study 10 minutes after completion of the resting dose infusion, to allow for sufficient Rb 82 decay;
- Administer a pharmacologic stress agent in accordance with its prescribing information;
- After administration of the pharmacologic stress agent, administer the second dose of Rb 82 at the time interval according to the prescribing information of the pharmacological stress agent;
- Start imaging 60-90 seconds after completion of the stress rubidium Rb 82 chloride dose infusion and acquire images for 3-7 minutes.

For Both Rest and Stress Imaging:

- If a longer circulation time is anticipated (e.g., in a patient with severe left ventricular dysfunction), start imaging 120 seconds after the rest dose.
- Acquisition may be started immediately post-injection if dynamic imaging is needed.

2.4 Elution System

- Use RUBY-FILL Rubidium Rb 82 Generator only with an elution system specifically designed for use with the generator (RUBY Rubidium Elution System) and capable of accurate measurement and delivery of doses of rubidium Rb 82 chloride injection.
- The generator used with the elution system provides ± 10% accuracy for rubidium Rb 82 chloride doses between 370-2220 MBq (10-60 mCi)
- Follow instructions in the RUBY Rubidium Elution System User Manual for the set up and intravenous infusion of rubidium Rb 82 chloride injection dose.

2.5 Directions for Eluting Rubidium Rb 82 Chloride Injection

- Allow at least 10 minutes between elutions for regeneration of Rb 82.
- Elute with additive-free 0.9% Sodium Chloride Injection USP only. Additives (particularly calcium ions, to which strontium ions are chemically analogous), may cause the release of substantial amounts of Sr 82 and/or Sr 85 into the eluate regardless of the age or prior use of the generator.
- The system will automatically discard the first 75 mL eluate each day the generator is first eluted.
- The RUBY Rubidium Elution System automatically generates records and saves data of all eluate volumes (from flushing, QC testing, patient infusions), representing the cumulative volume of eluate from the generator.

2.6 Eluate Testing Protocol

- **Elute with additive-free 0.9% Sodium Chloride Injection USP only.**
- Use the ionization chamber-type dose calibrator that is integrated into the elution system (used specifically with the RUBY-FILL Rubidium Rb 82 Generator) for eluate testing.

- Perform **Mandatory Eluate Testing** (i.e. Quality Control test) to determine Rb 82, Sr 82, and Sr 85 levels:
  1. Daily - Before administering rubidium Rb 82 chloride injection to the first patient each day.
  2. Repeat Every 4 patients after an **Alert Limit** has been detected.

     Alert Limits:

     - 20 L total elution volume has passed through the generator column, or
     - Sr 82 level reaches 0.004 μCi per mCi (kBq per MBq) Rb 82, or
     - Sr 85 level reaches 0.04 μCi per mCi (kBq per MBq) Rb 82.
  3. Immediately after detection of the volume alert limit (20 L).

- The elution system will automatically indicate when alert limits have been reached and require that additional tests be performed.

When the Quality Control test is performed as described in the User Manual, the system automatically performs the following eluate testing:

Rubidium Eluate Testing:

1. The dose calibrator is automatically set for Rb 82 within the Elution System.
2. The Quality Control test begins by automatically initiating a generator flush using 75 mL of 0.9% Sodium Chloride Injection USP. This eluate is by default diverted towards the waste container and is ultimately discarded.
3. After the generator flush, the system waits approximately 15.2 minutes to accomplish a complete generator recharge of 12 Rb 82 half-lives

4. The system then elutes a calibration sample (35 mL of 0.9% Sodium Chloride Injection USP at 20 mL/min). Using the dose calibrator, the system automatically quantifies the activity of Rb 82 in the calibration sample (Rb 82 decay does not need to be corrected for because of a real-time automated measurement).

Strontium Eluate Testing (Strontium Breakthrough):

1. Using the calibration sample obtained from the Rb 82 eluate testing, the system allows the sample to stand for 30 minutes to allow for the complete decay of Rb 82.
2. The system measures the activity of the sample to automatically determine the total Sr 82 and Sr 85 activity.
3. The system automatically determines the ratio (R) on the day (post calibration) of the measurement using the ratio of Sr 85/Sr 82 on the day of calibration provided on the generator label and the Sr 85/Sr 82 ratio factor from the Sr 85/Sr 82 ratio based on generator age using the following equation:

$$R = \frac{[\text{Sr 85}]}{[\text{Sr 82}]} \text{ on calibration date } X \text{ Ratio Factor on the day (post-calibration) of measurement}$$

4. The system uses a correction factor (F) of 0.48 to compensate for the contribution of Sr 85 to the reading.
5. The system calculates the amount of Sr 82 in the sample using the following equation:

In Empirical Units (μCi):

$$\text{Sr 82 (μCi)} = \frac{\text{dose calibration reading (μCi)}}{[1 + (R)(F)]}$$

Example: dose calibrator reading (μCi) = 0.8
Sr 85/Sr 82 ratio (R) = (1.48)
correction factor (F) = 0.48

$$\text{Sr 82 (μCi)} = \frac{0.8\ \mu\text{Ci}}{[1 + (1.48)(0.48)]} = 0.47\ \mu\text{Ci}$$

In International Units (kBq)

$$\text{Sr 82 (kBq)} = \frac{\text{dose calibration reading (μCi)}}{[1 + (R)(F)]}$$

Example: dose calibrator reading (kBq) = 29.6 kBq
Sr 85/Sr 82 ratio (R) = (1.48)
correction factor (F) = 0.48

$$\text{Sr 82 (kBq)} = \frac{29.6\ \text{kBq}}{[1 + (1.48)(0.48)]} = 17.3\ \text{kBq}$$

6. The system determines if Sr 82 in the eluate exceeds an Alert or Expiration Limit by dividing the μCi (or kBq) of Sr 82 by the mCi (or MBq) of Rb 82 at End of Elution (see below for further instructions based on the Sr 82 level)

In Empirical Units (μCi)

Example: 0.47 μCi of Sr 82; 50 mCi of Rb 82

$$\frac{0.47\ \mu\text{Ci Sr 82}}{50\ \text{mCi Rb 82}} = 0.0094\ \mu\text{Ci Sr 82/mCi Rb 82}$$

(Sr 82 is above Alert Limit of 0.004 μCi/mCi; additional daily eluate testing must be performed)

In International Units (kBq)

Example: 17.3 kBq of Sr 82; 1850 MBq of Rb 82

$$\frac{17.3\ \text{kBq Sr 82}}{1850\ \text{MBq Rb 82}} = 0.0094\ \text{kBq Sr 82/MBq Rb 82}$$

(Sr 82 is above Alert Limit of 0.004 kBq/MBq; additional daily eluate testing must be performed)

7. The system determines if Sr 85 in the eluate exceeds an Alert or Expiration Limit by multiplying the result obtained in step 6 by (R) as calculated in step 3 (above).

In Empirical Units (μCi)

Example: 0.0094 x 1.48 = 0.014 μCi Sr 85/mCi Rb 82

(Sr 85 test result is below Alert and Expiration Limits)

In International Units (kBq)

Example: 0.0094 x 1.48 = 0.014 kBq Sr 85/MBq Rb 82

(Sr 85 test result is below Alert and Expiration Limits)

The system uses Table 1 to calculate the decay factor for Rb 82

TABLE 1

Physical Decay Chart: Rb 82 half-life 75 seconds

Seconds	Fraction Remaining	Seconds	Fraction Remaining
0*	1.00	165	0.218
15	0.871	180	0.190
30	0.758	195	0.165
45	0.660	210	0.144
60	0.574	225	0.125
75	0.500	240	0.109
90	0.435	255	0.095
105	0.379	270	0.083
120	0.330	285	0.072
135	0.287	300	0.063
150	0.250		

*Elution time

The system uses Table 2 to calculate the ratio (R) of Sr 85/Sr 82.

TABLE 2

Sr 85/Sr 82 Ratio Chart (Sr 85 $T_{1/2}$ = 65 days, Sr 82 $T_{1/2}$ = 25 days)

Days	Ratio Factor	Days	Ratio Factor	Days	Ratio Factor
0*	1.00	21	1.43	42	2.05
1	1.02	22	1.46	43	2.08
2	1.03	23	1.48	44	2.12
3	1.05	24	1.51	45	2.15
4	1.07	25	1.53	46	2.19
5	1.09	26	1.56	47	2.23
6	1.11	27	1.58	48	2.27
7	1.13	28	1.61	49	2.30
8	1.15	29	1.64	50	2.34
9	1.17	30	1.67	51	2.38
10	1.19	31	1.70	52	2.43
11	1.21	32	1.73	53	2.47
12	1.23	33	1.76	54	2.51
13	1.25	34	1.79	55	2.55
14	1.27	35	1.82	56	2.60
15	1.29	36	1.85	57	2.64
16	1.31	37	1.88	58	2.69
17	1.34	38	1.91	59	2.73
18	1.36	39	1.95	60	2.78
19	1.38	40	1.98		
20	1.41	41	2.01		

* Day of calibration.

2.7 RUBY-FILL Expiration

Stop use of the RUBY-FILL Rubidium Rb 82 Generator once any one of the following **Expiration Limits** is reached:

- A total elution volume of 30 L has passed through the generator column, or
- Expiration date of the generator (60 days post-manufacturing), or
- An eluate Sr 82 level of 0.01 µCi/mCi (kBq/MBq) Rb 82, or
- An eluate Sr 85 level of 0.1 µCi/mCi (kBq/MBq) Rb 82.

2.8 RUBY-FILL Dose Delivery Limit

The maximum available activity (delivery limit) will decrease as the generator ages. Certain doses, including the maximum recommended dose [60 mCi (2220 MBq)], are not achievable for the entire shelf-life of the generator. Table 3 provides an estimate of the maximum available activity of Rubidium Rb 82 (Delivery Limit) as a function of generator age.

Table 3 Rubidium Rb 82 Dose Delivery Limit Based on Generator Age[1]

Generator Age (days) [2]	Maximum Rubidium Dose (Delivery Limit)
0-17	60 mCi (2220 MBq)
24	50 mCi (1850 MBq)
32	40 mCi (1480 MBq)
42	30 mCi (1110 MBq)
57	20 mCi (740 MBq)

[1]Estimate is based on a 100 mCi (3700 MBq) Sr 82 generator at calibration.

[2]Generator age at which delivery limit is reached varies with generator activity at release. For example, an 85 mCi (3145 MBq) generator and a 115 mCi (4255 MBq) generator will reach a delivery limit <60 mCi at ≥ 12 days and ≥ 23 days, respectively.

2.9 Radiation Dosimetry

The estimated radiation absorbed dose coefficients for Rb 82, Sr 82, and Sr 85 from an intravenous injection of rubidium Rb 82 chloride are shown in Table 4.

Table 4
Adult absorbed dose per radioisotope activity associated with injection

Organ	^{82}Rb[1] (µGy/MBq)	^{82}Sr[2] (µGy/kBq)	^{85}Sr[2] (µGy/kBq)
Adrenals	2.4	2.9	1.4
Bone surfaces	0.42	29	2.7
Brain	0.14	2.2	0.8
Breast	0.19	1.9	0.5
Gallbladder wall	0.72	2.3	0.8
Gastrointestinal tract			
Esophagus[3]	1.5	2.1	0.6
Stomach wall	0.83	2.1	0.6
Small intestine wall	2.0	2.6	1.1
Colon wall	1.1	9.7	1.2
(ULI wall)	1.1	6.4	1.0
(LLI wall)	1.1	14	1.4
Heart wall	4.0	2.2	0.7
Kidneys	9.3	2.5	0.7
Liver	1.0	2.2	0.7
Lungs	2.6	2.2	0.8
Muscles	0.23	2.2	0.7
Ovaries	0.50	2.8	1.2
Pancreas	2.6	2.5	0.9
Red marrow	0.38	25	2.7
Skin	0.18	1.9	0.5
Spleen	0.18	2.2	0.7

Testes	0.26	2.0	0.5
Thymus	1.5	2.1	0.6
Thyroid	0.31	2.2	0.7
Urinary bladder wall	0.18	5.9	0.8
Uterus	1.0	2.5	0.9
Remaining organs	0.31	-	-
Effective dose per unit activity	1.1 µSv/MBq	6.3 µSv/kBq	1.1 µSv/kBq

[1] Rb- 82 doses are averages of rest and stress dosimetry data. To calculate organ doses (µGy) from Rb- 82, multiply the dose coefficient for each organ by the administered activity in MBq.
[2] To calculate organ doses attributable to Sr-82 and Sr-85, multiply those dose coefficients by the respective strontium activities associated with the injection.
[3] The absorbed dose to the thymus is used as a substitute.

3 DOSAGE FORMS AND STRENGTHS

RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. RUBY-FILL consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145 - 4255 MBq (85 - 115 mCi) Sr 82 at calibration time.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Unintended Sr 82 and Sr 85 Radiation Exposure

Unintended radiation exposure occurs when the Sr 82 and Sr 85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits. To minimize the risk of unintended radiation exposure, strict adherence to a daily eluate testing protocol is required. Stop using the rubidium generator when the expiration limits are reached *[see Dosage and Administration (2.6) and (2.7)]*.

5.2 Risks Associated with Pharmacologic Stress

Pharmacologic induction of cardiovascular stress may be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform pharmacologic stress testing in accordance with the pharmacologic stress agent's prescribing information and only in the setting where cardiac resuscitation equipment and trained staff are readily available.

5.3 Radiation Risks

RUBY-FILL use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care providers. Encourage patients to void as soon as a study is completed and as often as possible thereafter for at least one hour *[see Dosage and Administration (2.1) and (2.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reaction associated with the use of rubidium Rb 82 chloride was identified in clinical trials or post marketing reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Unintended Sr 82 and Sr 85 Radiation Exposure: Unintended radiation exposure has occurred in some patients who received rubidium Rb 82 chloride injection at clinical sites where generator eluate testing appeared insufficient *[see Boxed Warning, Warnings and Precautions (5.1), Dosage and Administration (2.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on the use of rubidium Rb 82 in pregnant women. Animal reproduction studies with rubidium Rb 82 chloride have not been conducted. However, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering rubidium Rb 82 chloride injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from Rb 82 and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Rb 82 chloride in human milk, the effects on the breastfed infant or the effects on milk production. Due to the short half-life of Rb 82 chloride (75 seconds), exposure of a breast fed infant through breast milk can be minimized by temporary discontinuation of breastfeeding [See Clinical Considerations]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rb 82, any potential adverse effects on the breastfed child from Rb 82 or from the underlying maternal condition.

Clinical considerations

Minimizing Exposure

Exposure to Rb 82 chloride through breast milk can be minimized if breastfeeding is discontinued when Rb 82 chloride injection is administered. Do not resume breastfeeding until at least one hour after completion of RUBY-FILL infusion.

8.4 Pediatric Use

The safety and effectiveness of rubidium Rb 82 chloride injection in pediatric patients have not been established.

8.5 Geriatric Use

In elderly patients with a clinically important decrease in cardiac function, lengthen the delay between infusion and image acquisition *[see Dosage and Administration (2.3)]*. Observe for the possibility of fluid overload from the infusion.

11 DESCRIPTION

11.1 Chemical Characteristics

RUBY-FILL Rubidium Rb 82 Generator contains accelerator-produced Sr 82 adsorbed on stannic oxide in a lead-shielded column and provides a means for obtaining sterile non-pyrogenic solutions of rubidium Rb 82 chloride injection. The chemical form of Rb 82 is ^{82}RbCl.

The amount (mCi) of Rb 82 obtained in each elution will depend on the potency of the generator. When used with the RUBY Rubidium Elution System, the generator provides ± 10% accuracy for rubidium Rb 82 chloride doses between 370-2220 MBq (10-60 mCi).

When eluted at a rate of 15 - 30 mL/minute, each generator eluate at the end of elution should not contain more than 0.02 μCi (0.74 kBq) of Sr 82 and not more than 0.2 μCi (7.4 kBq) of Sr 85 per mCi of rubidium Rb 82 chloride injection, and not more than 1 μg of tin per mL of eluate.

11.2 Physical Characteristics

Rb 82 decays by positron emission and associated gamma emission with a physical half-life of 75 seconds. Table 5 shows the annihilation photons released following positron emission which are useful for detection and imaging studies.

The decay modes of Rb 82 are: 95.5% by positron emission, resulting in the production of annihilation radiation, i.e., two 511 keV gamma rays; and 4.5% by electron capture, resulting in the emission of "prompt" gamma rays of predominantly 776.5 keV. Both decay modes lead directly to the formation of stable Kr 82.

TABLE 5
Principal Radiation Emission Data

Radiation	Mean Percent Per Disintegration	Mean Energy (keV)
Annihilation photons (2)	191.01	511 (each)
Gamma rays	13 to 15	776.5

The specific gamma ray constant for Rb-82 is 6.33 R cm^2 / mCi h (1.23×10^{-12} C m^2 / kg MBq s). The first half-value layer is 0.53 cm of lead (Pb). Table 6 shows a range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb. For example, the use of a 6.15 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE 6
Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Attenuation Factor
0.53	0.5
1.68	10^{-1}
3.55	10^{-2}
6.15	10^{-3}
9.3	10^{-4}

Sr 82 (half-life of 25 days; 600 hrs.) decays to Rb 82. To correct for physical decay of Sr 82, Table 7 shows the fractions that remain at selected intervals after the time of calibration.

TABLE 7
Physical Decay Chart: Sr 82 half-life 25 days

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
0*	1.000	21	0.559	41	0.321
1	0.973	22	0.543	42	0.312
2	0.946	23	0.529	43	0.304
3	0.920	24	0.514	44	0.295
4	0.895	25	0.500	45	0.287
5	0.871	26	0.486	46	0.279
6	0.847	27	0.473	47	0.272
7	0.824	28	0.460	48	0.264
8	0.801	29	0.448	49	0.257
9	0.779	30	0.435	50	0.250
10	0.758	31	0.423	51	0.243
11	0.737	32	0.412	52	0.237
12	0.717	33	0.401	53	0.230
13	0.697	34	0.390	54	0.224
14	0.678	35	0.379	55	0.218
15	0.660	36	0.369	56	0.212
16	0.642	37	0.358	57	0.206
17	0.624	38	0.349	58	0.200
18	0.607	39	0.339	59	0.195
19	0.591	40	0.330	60	0.189
20	0.574				

* Calibration time

To correct for physical decay of Rb 82, Table 1 shows the fraction of Rb 82 remaining in all 15 second intervals up to 300 seconds after time of calibration *[see Dosage and Administration (2.6)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rb 82 is analogous to potassium ion (K^+) in its biochemical behavior and is rapidly extracted by the myocardium proportional to the blood flow. Rb^+ participates in the sodium-potassium (Na^+/K^+) ion exchange pumps that are present in cell membranes. The intracellular uptake of Rb 82 requires maintenance of ionic gradient across cell membranes. Rb 82 radioactivity in viable myocardium is higher than in infarcted tissue, reflecting intracellular retention.

12.2 Pharmacodynamics

In human studies, myocardial activity was noted within the first minute after peripheral intravenous injection of Rb 82. When areas of infarction or ischemia are present in the myocardium, they are visualized within 2-7 minutes after injection as photon-deficient, or "cold", areas on the myocardial perfusion scan. In patients with reduced cardiac function, transit of the injected dose from the peripheral infusion site to the myocardium may be delayed.

Blood flow brings Rb 82 to all areas of the body during the first pass of circulation. Accordingly, visible uptake is observed in highly vascularized organs, such as the kidneys, liver, spleen and lungs.

12.3 Pharmacokinetics

With a physical half-life of 75 seconds, Rb 82 is converted by radioactive decay into stable Kr 82 gas, which is passively expired by the lungs.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 chloride injection may affect fertility in males or females.

14 CLINICAL STUDIES

In a descriptive, prospective, blinded image interpretation study of adult patients with known or suspected coronary artery disease, myocardial perfusion deficits in stress and rest PET images obtained with ammonia N 13 (n = 111) or Rb 82 (n = 82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a scale of 0 (normal) to 5 (severe). Values for stenosis flow reserve, defined as flow at maximum coronary vasodilatation relative to rest flow, ranged from 0 (total occlusion) to 5 (normal). With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

A systematic review of published literature was conducted using pre-defined inclusion/exclusion criteria which resulted in identification of 10 studies evaluating the use of Rb 82 PET myocardial perfusion imaging (MPI) for the identification of coronary artery disease as defined by catheter-based angiography. In these studies, the patient was the unit of analysis and 50% stenosis was the threshold for clinically significant coronary artery disease (CAD). Of these 10 studies, 9 studies were included in a meta-analysis for sensitivity (excluding one study with 100% sensitivity) and 7 studies were included in a meta-analysis of specificity (excluding 3 studies with 100% specificity). A random effects model yielded overall estimates of sensitivity and specificity of 92% (95% CI: 89% to 95%) and 81% (95% CI: 76% to 86%), respectively. The use of meta-analysis in establishing performance characteristics is limited, particularly by the possibility of publication bias (positive results being more likely to be published than negative results) which is difficult to detect especially when based on a limited number of small studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RUBY-FILL Rubidium Rb 82 Generator consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145 – 4255 MBq (85 - 115 mCi) Sr 82 at calibration time. A lead shield encases the generator. The container label provides complete assay data for each generator. Use RUBY-FILL Rubidium Rb 82 Generator only with an appropriate, properly calibrated Elution System (RUBY Rubidium Elution System) labeled for use with the generator.

16.2 Storage and Handling

- Store the generator at 20-25 ºC (68-77 ºF).
- Receipt, transfer, possession, storage, disposal or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission (NRC), Agreement States or Licensing States as appropriate. Do not dispose of the generator in regular refuse systems.
- For questions about the disposal of the RUBY-FILL Rubidium Rb 82 Generator, contact Jubilant Draximage Inc. at 1-888-633-5343.

17 PATIENT COUNSELING INFORMATION

Pregnancy
Advise a pregnant woman of the potential risk to a fetus.

Lactation
Advise lactating women that exposure to Rb 82 chloride through breast milk can be minimized if breastfeeding is discontinued when Rb 82 chloride injection is administered. Advise lactating women not to resume breastfeeding for at least one hour after completion of rubidium Rb 82 infusion.

General Safety Precautions
Advise patients to void after completion of each image acquisition session and as often as possible for one hour after completion of the PET scan.

Manufactured by:

Jubilant DRAXIMAGE Inc.
16751 TransCanada Highway
Kirkland, Québec, Canada
H9H 4J4

Version: 1

Rx only
For elution of sterile nonpyrogenic Rubidium Chloride Rb 82

Generator column contains Strontium-82 adsorbed on anhydrous stannic oxide.

Usual Dosage: See package insert.

Directions for use: See package insert.

Store at 20 – 25 °C (68 – 77 °F)
[See USP Controlled Room Temperature]

RUBY FILL
RUBIDIUM Rb82 GENERATOR

85-115 mCi

Diagnostic Agent for Intravenous Use

CAUTION

RADIOACTIVE
MATERIAL

Must be handled only by qualified personnel in conformity with regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.
WARNING: maintain proper radiation safety precautions at all time.

Generator column must not be removed from lead shield.

Manufactured by:
Jubilant DRAXIMAGE Inc.
16751 Trans-Canada Highway
Kirkland, QC H9H 4J4, Canada

Confidential

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

/s/

LIBERO L MARZELLA
09/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	9/29/2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	202153
Applicant Name	Jubilant DraxImage, Inc.
Dates of Submission	June 18, 2010, resubmitted on 12/30/2015 as Class 2
PDUFA Goal Date	6/30/2016, extended to 9/30/2016 due to a major amendment on 6/11/2016
Proprietary Name **Established (USAN) Name**	Ruby-Fill (Rubidium Rb 82 Generator) Rubidium chloride Rb 82
Dosage Form **Strength**	Sterile solution for intravenous injection. The generator contains between 85 and 115 mCi of Sr82. When eluted at a rate between 15 and 30mL/min, the generator delivers a single dose between 10 and 60mCi of 82RbCl injection at a maximum volume of 60mL per infusion.
Indication	Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
<u>Product Quality</u> ONDP/Division II/Branch VI (Drug substance, Drug Product, Process, DMF) OPQ/OPF (Microbiology) OPQ/OPF/DBP/BI (Facilities) OPS/OGD (Microbiology, Regulatory)	AnneMarie Russell PhD, David Place PhD, Milagros Salazar PhD, and Eldon Leutzinger PhD Yeissa ChabrierRosello PhD and Jessica Cole PhD Michael Klapal Dupeh Palmer PhD, and Martin Shimer
<u>Devices</u> CDRH/GHDB DRH (Radiological Health)	Robert Myers, Ryan McGowan , Sarah Mollo, Donald Witters, Michael Long, Joseph Jorgens, and Alan Stevens Andrew Kang MD
<u>Clinical</u> DMIP: CDTL Labeling	Ira Krefting MD Michele Fedowitz MD
DMEPA	Michelle Rutledge PharmD, Yelena Maslov Pharm D, and QuynhNhu Nguyen MS

CDRH: Center for Devices and Radiological Health
CDTL- Cross Discipline Team Leader
CMC - Chemistry Manufacturing and Controls
DMF - Drug Master File
DMEPA - Division of Medication Error Prevention and Analysis
GHDB - General Hospital Devices Branch
OGD - Office of Generic Drugs
ONDP - Office of New Drug Products
OPQ - Office of Pharmaceutical Quality
OPS - Office of Pharmaceutical Science

1. Introduction

This review summarizes my assessment of the approvability of this application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. .

Product

Ruby-Fill is a Strontium 82/Rubidium 82 (Sr82/Rb82) generator and drug infusion and delivery system (Ruby elution system, [redacted] (b) (4)) that provide an eluted solution of the drug substance Rubidium Rb82 Chloride in sterile additive free 0.9% saline. The generator contains between 85 and 115 mCi of Sr82 at calibration time.

The complete system is composed of a saline bag [redacted] (b) (4) Rb-82 generator column, [redacted] (b) (4) and radiation calibrator system. The radionuclide generator contains Sr82 chloride adsorbed onto hydrous [redacted] (b) (4) stannic oxide packed in a column. The generator eluate containing Rb82 Cl has a stand-alone indication for Positron Emission Tomography (PET) imaging of the myocardium to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease. For these reasons the rubidium Rb82 generator is defined as a PET drug and is regulated under 21 CFR 212. The various components of the drug product delivery system, with the exception of the dose calibrator, are also are also regulated as drugs.

Rb82 decays by positron emission with a half-life of 1.3 minutes to stable krypton gas. Due the short Rb82 half-life the generator with its drug infusion system is designed to deliver promptly an injection of the Rb82Cl eluate.

Regulatory History

The manufacturer, Jubilant Draximage, submitted the original application on June 18, 2010 to the Office of Generic Drugs (OGD) as an abbreviated new drug application (ANDA). The drug product is Ruby-Fill a Sr82/Rb82 generator and drug infusion and delivery system. The Applicant referenced as the listed drug CardioGen-82 a Sr82/Rb82 generator containing 90-150 mCi of Sr 82 and marketed by Bracco Diagnostics under NDA 019414. FDA approved the reference listed drug in 1989.

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The final product is rubidium chloride Rb 82 Injection USP solution administered to a patient by infusion. The product (b) (4) contains the active ingredient, rubidium Rb82 chloride (b) (4) and the inactive ingredient 0.9% sodium chloride.

OGD's Division of Legal and Regulatory Support (Martin Shimer) determined on November 16, 2012 that the application was not eligible for submission under 505(j) because the proposed conditions of use of Ruby-Fill are not the same as those of the proposed RLD due to differences in the rates of infusion ((b) (4) ml/min vs. 50 ml/min) and total volumes (maximum of 60 ml vs.100 ml) of the drug product. The ONDP CMC reviewer (Dr. Leutzinger) in a December 12, 2012 memorandum underscored the importance of this difference. The potential for medication error existed if the incorrect rate of infusion specified for a Cardiogen-82 generator were used for the RubyFill generator.

As a result of this finding, the applicant submitted on January 17, 2013 a request for conversion of ANDA 202153 to NDA 202153 under the 505(b)(2) regulations. On January 15, 2013 OGD confirmed that the Office would continue to review the application using its authority to approve 505(b)(2) applications. Finally on September 17, 2014 OGD informed the applicant that DMIP would take the lead in the review of the NDA.

On December 18, 2014 FDA issued a Complete Response letter. The letter included a complete listing of the deficiencies in the application and recommendations to the applicant for addressing them. The major deficiencies involved: human factor study reports and adequacy of user training program; protocols for stability testing of the generator; elution system description and specifications, hazard analysis and safety requirements, performance and reliability, software verification and validation. Sterility assurance was another critical deficiency because of lack of demonstration of control of the risk of cross contamination (b) (4)

On December 15, 2015 FDA received a Class 2 resubmission. On June 30, 2016 FDA received a major amendment to the application and extended the review goal date to September 30, 2016.

2. Chemistry Manufacturing and Controls

Product Quality

I concur with the recommendation by the FDA CMC reviewer Dr. Russell that the application be approved from the standpoint of Chemistry, Manufacturing and Controls.

I concur with the assessment by the FDA Microbiology reviewers Dr. Chabrier-Rosello and Dr. Cole that the Applicant has addressed the Microbiology quality deficiencies. I concur that on the basis of acceptable sterility assurance, the application can be approved.

I note that the deficiencies identified by the FDA Chemistry Manufacturing and Controls reviewer Dr. Place regarding the level of post–approval testing proposed (b) (4) have been adequately addressed in the present submission

I reference my earlier concurrence with the findings by the FDA CMC reviewer Dr. Salazar who evaluated the manufacturing processes under DMF (b) (4) and found them to be adequate.

I reference my concurrence with the assessment on May 27, 2011 by the FDA Microbiology reviewer Dr. Palmer that the applicant has demonstrated an adequate level of sterility assurance for the manufacturing process of the generator.

Ruby-Fill Critical Quality Attributes: CMC

Ruby-Fill and its RLD Cardiogen-82 use hydrous stannic oxide as column matrix, and the separation is of the same chemical system (82Sr2+ / 82Rb+). Ruby-Fill differs from the RLD (b) (4)

The specifications for the radionuclide purity of the generator eluate are critical quality attributes for the safety and efficacy of Ruby-Fill. The labeling defines the expiry limits for safe and effective use of the generator. (b) (4)

The CMC reviewer verified the system's performance over the life-time of the generator for the recommended doses, the capability of the dose calibrator to detect strontium at alert levels for the low (10 mCi) dose, and the generator elution volume expiry of 30L. The reviewer requested incorporation of a new flow rate limit (15 mL) in the Ruby-Fill elution system and clear display of current maximum deliverable Rb82Cl dose. The latter provision was considered important for use in patient scheduling and weight based dosing.

Ruby-Fill Critical Quality Attributes: Microbiological

The figure below shows the Ruby-Fill elution system (as diagrammed by the applicant) with emphasis on the fluid path for the administration of Rb82 Cl injection. The potential for a breach in in sterility assurance of the drug product during installation and use including the potential for cross-contamination was an important concern evaluated by the FDA Microbiology reviewers.

The FDA reviewers considered the microbial contamination risks and the following mitigation steps: (b) (4) These steps were considered adequate.

However the results of initial testing did not fully support the adequacy of the mitigation steps. In particular the FDA reviewers requested that the applicant provide additional data on the functionality of the components (b) (4) to prevent patient to patient contamination. The applicant conducted additional validation studies (b) (4) using a dye ingress methodology, positive controls, and simulated worst case conditions. I agree with the Microbiology reviewers that the validation study results show the risk of cross-contamination (b) (4) is well controlled (b) (4)

Device Components

I concur with the assessment by the Mechanical Engineering reviewer Robert Meyer of the General Hospital Devices Branch that the device constituents of Ruby-Fill (Ruby Rubidium Elution System (b) (4)) are acceptable.

I concur with the assessment by the FDA Biocompatibility reviewer Sarah Mollo that the testing of the Ruby-Fill fluid path assembly is adequate and the results are acceptable.

I concur with the conclusions by the FDA reviewers Donald Witters and Michael Long that the electrical and EMC safety of the device are acceptable.

I concur with the assessment by the FDA software reviewer Joseph Jorgens that the software is verified adequately and is acceptable.

I reference my concurrence with Dr. Andrew Kang's May 29, 2014 review of the validation study to assess the accuracy of the break-through testing. The FDA reviewer found the generator breakthrough testing procedure to be acceptable.

The Ruby Elution System is a mobile cart that houses all the components required for the measurement and intravenous infusion of rubidium 82 chloride injection. The system includes a computer (b) (4) generator well, shielding, eluate radioactivity counter, dose calibrator (b) (4)

(b) (4)

In the previous review cycle, the FDA reviewers identified several critical device deficiencies regarding requirements and specifications of the infusion system, performance testing and risk analyses, software analyses, compliance with sterility, biocompatibility and electrical safety, and electromagnetic compatibility standards.

I reference Robert Myer's primary review for the detailed assessment of the applicant's response to each of these deficiencies. I agree with the reviewer's assessment that the deficiencies have been adequately addressed.

The applicant has provided specifications for the Elution System hardware and software performance, usability, and safety. The FDA reviewers examined all the technical specifications, the protocols for testing, the summary of test results and the traceability matrix relating requirements to verification reports for each specific system component. The reviewer determined that the testing methods used and the results are generally acceptable.

In particular, the FDA reviewers examined the quality control testing of Rb82Cl injection conducted to demonstrate the functionality of the generator and elution system under simulated clinical conditions. This testing included the satisfactory verification of the specified accuracy for Rb82Cl dose, volume administered, flow-rate, and elution time. Of critical importance was the verification of the accuracy of the Elution System to detect strontium breakthrough within the specified limits. The FDA reviewers also determined that the testing and results (b) (4) was acceptable. The applicant's risk analysis was also considered adequate.

3. Nonclinical Pharmacology and Toxicology

The applicant did not include nonclinical studies and this submission does not require additional nonclinical data.

4. Clinical Pharmacology and Biopharmaceutics

There is no new clinical pharmacology information in this NDA and none is needed.

5. Clinical Microbiology

This section is not applicable to this NDA.

6. Clinical/Statistical Efficacy

The submission does not include any new efficacy data and none are needed because the Rb82 Cl drug products are identical.

7. Safety

The critical safety issue with Sr82/Rb82 generators is the potential for breakthrough of Sr82 and Sr85. For this reason daily testing of the generator eluate is needed; more intensive testing is needed after small amounts of Sr are detected (alert level) in the eluate. Expiry of the generator is defined by specified level of Sr82 and Sr 85 breakthrough.

The following are the essential labeling specifications for the safe use of the generator.

- Do not exceed a single dose of 2220 MBq (60 mCi)
- Stop use of a generator at an Expiration Limit of:
  - 30 L for the generator's cumulative eluate volume, or
  - 60 days post generator calibration date, or
  - An eluate Sr-82 level of 0.01 µCi /mCi Rb-82, or
  - An eluate Sr-85 level of 0.1 µCi /mCi Rb-82
- Do not exceed a total infusion volume of 60 mL

Rubidium Rb 82 chloride is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration. The use of the radiopharmaceutical contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Labeling mitigates these risks by the following measures: stressing the need for safe handling to minimize radiation exposure to the patient and health care providers; encouraging patients to void as soon as a study is completed; providing organ dosimetry data to estimate radiation absorbed doses; recommending weight-based dosing, and recommending a new lower dose limit.

Myocardial perfusion imaging using Rb82Cl requires the pharmacologic induction of cardiac stress. The stress testing is associated with serious adverse reactions in patients with coronary artery disease. Availability of resuscitation equipment and staff are recommended in labeling to mitigate risk.

Human Factors Studies

I concur with the FDA reviewers' assessment that the deficiencies that prevented the verification of the adequacy of the human factor testing and user training have been addressed in the present submission.

The FDA reviewers determined that the Applicants' methodology of the human factors study in terms of objectives, training provided, use environment, tasks tested are acceptable. The study demonstrated that users who receive training are able to use the product safely and effectively. Ruby-Fill contains multiple components including generator, elution system, (b) (4) Specialized training will occur for each person using Ruby-Fill and will be identical to the training that occurred on the validation human factors study. Training will include all the necessary steps for safe and effective product use. Hands-on demonstrations will be used in the training and successful completion of a test will be required. Upon completion of the training, the intended user will receive a certificate.

8. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

9. Pediatrics

No pediatric plan was needed for this application because of the initial date of the submission and no plan was provided. The application does not trigger PREA and no pediatric study is planned.

10. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis

I concur with the assessment by the DMEPA reviewer (Dr. Rutledge) on April 1, 2014 that the proposed proprietary name Ruby-Fill is acceptable. Labeling recommendations by the reviewers were accepted by the applicant.

Office of Compliance

I concur with the assessment by Michael Klapal of the Office of Compliance that all the facilities are acceptable to support approval of the application.

There are no significant or outstanding risks to the manufacturing process or final product based on the evaluation of the listed facilities' inspection results, inspectional history, and relevant experience. The Office of Compliance performed the most recent inspection of the facility for manufacturing, release, packaging, labeling, and stability testing of commercial batches of rubidium generator at Jubilant Draximage Inc. (JDI) on 12/17/2015. This facility is considered acceptable for use in the present NDA.

Jubilant Hollister Stier General Partnership (JHS), Canada conducts testing of raw materials, and sterility and endotoxin testing for JDI's finished products. Based on review of previous inspectional findings the facility is considered acceptable.

The Office of Compliance also reviewed the history of inspectional findings for the following control testing laboratories facilities: (b) (4) Each facility was determined to be acceptable.

Labeling Review

I concur with the assessment by Dr. Michele Fedowitz (Associate Director for Labeling) that the Prescribing Information (PI) in its present form is acceptable.

Dr. Fedowitz notes that the major revisions to the PI included changing the format to be consistent with the Pregnancy and Lactation Labeling Rule, and changing the dosage and administration section to provide for weight-adjusted dosing with a lower dosage limit. The recommended dosage is between 10 and 30 Megabecquerels per kg (0.27 to 0.81 millicuries per kg). The review team verified that the comprehensive review of the scientific literature provided by the applicant contained sufficient support for changing the recommended dosing to weight-based

dosing and that Ruby-Fill could deliver the recommended range of doses including a dose as low as 10 mCi. Advances in PET image acquisition technology have made possible the use of lower doses for cardiac visualization and lower doses are consistent with the aim of reducing exposure to radiation to as low as reasonably achievable.

I concur with the assessment by the CMC reviewer Dr. Russell that as revised the User Manual is acceptable. The revisions to the user manual included flow-rate lower limits (15 mL/min), Rb82 delivery activity lower limit (10 mCi) and display of current maximum deliverable dose. The description and sourcing of supplies in the manual were clarified.

Postmarketing Commitments, Other Risk Management Steps
I concur with the FDA reviewer's assessment that none are needed.

11. Decision/Risk Benefit Assessment

I concur with the unanimous recommendation by the FDA reviewers that Ruby-Fill be approved.

In the present application the manufacturer has addressed the deficiencies identified in FDA's complete response letter dated December 18, 2014. The deficiencies included requirements and specifications of the infusion system, performance testing and risk analyses, software analyses, compliance with sterility, biocompatibility and electrical safety and electromagnetic compatibility standards, human factor studies, training program for the users and a testing program for post-approval (b) (4)

I concur with the assessment by the CDTL reviewer, Dr. Krefting, that Rb82Cl remains a valuable diagnostic radiopharmaceutical for use in PET myocardial perfusion imaging at rest and stress in patients with suspected or existing coronary disease. The risk/benefit of the radiopharmaceutical remains unchanged.

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/s/

LIBERO L MARZELLA
09/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 202153
Ruby-Fill® (RUBIDIUM Rb- 82 CHLORIDE)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Alan Stevens
Andrew Kang
Anne Marie Russell
Danae Christodoulou
Dat Doan
David Place
Donald Witters Jr.
Dupeh Palmer
Eldon Leutzinger
Eric Duffy
Frank Lutterodt
Ira Krefting
Jane Liedtka
Jessica Cole
Joseph Jorgens III
Kyong (Kaye) Kang
Libero Marzella
Lubna Merchant
Lynne Ensor
Martin Shimer
Meena Ramachandra
Michele Fedowitz
Neil Vora
Robert Meyer
Rong Wang
Sarah Mollo
Stanley Stern
Yeissa Chabrier-Rosello

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Sept. 8, 2016
From	Ira Krefting, M.D.
Subject	Cross-Discipline Team Leader Review
NDA Supplement#	202-153
Applicant	Jubilant Draximage
Date of Submission	June 18, 2010
PDUFA Goal Date	Sept. 30, 2016
Proprietary Name / Non-Proprietary Name	Ruby Fill/ Rubidium 82
Dosage form(s) / Strength(s)	Intravenous dosing 10-30 Megabecquerels (Mbq)/kg [0.27-0.81 millicuries (mCi/kg)]
Applicant Proposed Indication(s)/Population(s)	RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease. Population: Adult patients
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as the applicant's proposal

Benefit-Risk Summary and Assessment

The Ruby-Fill generator and infusion system provides an improvement in the imaging modalities currently available to aide in the diagnosis of coronary artery disease. Coronary artery disease is a significant, ubiquitous public health concern and prompt, accurate diagnosis to facilitate early treatment is important. Another Rubidium generator, CardioGen (during the initial submission and review cycle - designated as the Reference Listed Drug – RLD), was approved in 1989, so there is extensive clinical experience with Rubidium 82 cardiac imaging. The major safety concern with Rubidium generators is the inadvertent release of excess radioactive Strontium, the Rubidium 82 parent, into an administered dose of Rubidium 82 (called: "breakthrough" see below). Advances in PET imaging devices and extensive clinical experience, allowed for approval of weight based dosing methodology for Ruby-Fill, whereas the RLD had a general dosing recommendation. Potential microbiologic egress and the inability of the Ruby-Fill to deliver the labeled dosing range through its life cycle were specific review issues which were successfully resolved.

Rubidium 82 with a 75 second half life is intravenously infused into a patient being evaluated for coronary artery disease. Since Rubidium has similar chemical and physical characteristics to Potassium, Rubidium as if were Potassium, will be taken up by viable cardiac cells; obstructed coronary vessels and dead cardiac will not show this uptake. Positrons emitted as Rubidium 82 decays will be imaged by PET, Positron Emission Tomography, outlining vascular regions of obstruction and infarction.
Rubidium 82 PET cardiac images are considered by some clinicians to be clearer than SPECT cardiac images. Ruby-Fill provides Rubidium 82, the identical imaging drug produced by CardioGen. The PET images produced with the Rubidium 82 from Ruby-Fill should be of the same quality as those from CardioGen and for which there is extensive clinical experience. The radiation exposure with Rubidium is lower than the exposure with SPECT agents. (b) (4)

Over the course of the NDA review the major safety concerns and undeliverable dosing issue were evaluated and resolved:

Regarding excess Strontium (breakthrough) in the eluate: All Rubidium generators have a small, allowable amount of Strontium 82 and 85 in the eluate administered to the patient. (b) (4) Ruby-Fill employs a computerized system of daily testing to monitor the level of Strontium in the eluate. Strontium may deposit in bone and with its long half life mayincrease the radiation exposure of patients (b) (4) re-testing for Strontium "breakthrough" is automatically performed after every 4 patients. (b) (4) Generators are also removed from service when 30 liters of saline have passed through them or after 60 days. (b) (4)

(b) (4)

Regarding microbiologic concerns: Microbiologic contamination risk was investigated by a dye study recommended by the microbiology reviewers. The reviewers designed a study with the sponsor (b) (4) Data from this study led the microbiology reviewers to conclude the microbiological safety of Ruby-Fill is acceptable.

Regarding an undeliverable labeled dose: Detailed review of the generator output testing by the CMC staff led to the finding that Ruby-Fill in clinical use could not reliably produce the Rubidium doses in the upper range of the proposed labeled dosing (60 mCi) as the generator aged toward expiration. The older the generator, the smaller the maximum dose it can produce. Therefore heavier patients requiring higher Rubidium doses could not be adequately imaged with the Rubidium 82 output from an older generator. This limitation has been added to labeling. The sponsor has also demonstrated that the generator can also produce the low dose of 10 mCi.

In toto, Ruby-Fill provides a safe modality for imaging patients with suspected or clinically diagnosed coronary artery disease. The major safety concern of Strontium breakthrough has been dealt with through a vigorous Strontium monitoring requirement which has proven effective when instituted for CardioGen; computerization in Ruby-Fill has made the monitoring process more efficient. (b) (4) The risk of microbiologic contamination has beencontrolled. Dosing limitations by generator age have been added to the label and instructions for use manual to minimize the risk that patients requiring a high Rubidium dose will be unable to undergo a scheduled imaging study due to the inability of the generator to produce that dose. New dosing recommendations are now weight based.

The review team has determined that the Ruby-Fill pharmaceutical quality is acceptable and the risks of, Strontium breakthrough and microbiologic ingress, haveadequately controlled. The risk benefit ratio is favorable and Ruby-Fill is recommended by the CDTL for approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Coronary artery disease evaluation	**No new clinical data was presented in the NDA. However, the RLD, CardioGen approved in 1989, has been useful in the evaluation of coronary artery disease. Since both generators are systems for the production of Rubidium 82, equal utility is expected from Ruby-Fill**
Current Treatment Options	Myocardial perfusion imaging CardioGen • SPECT scans • Exercise testing	Ruby-Fill is useful for the evaluation of myocardial perfusion in patients with known or suspectedcoronary artery disease.
Benefit	• Less radiation exposure compared to radioactive imaging agents used with SPECT scan • PET scans havegood image quality and acceptable diagnostic performance	Ruby-Fill is a Rubidium 82 generator with a design that limits the potential for radioactive Strontium 82, the parent of Rubidium, to enter the dose administered to a coronary imaging patient
Risk	• Undiagnosed coronary artery disease • Unintended radiation exposure to Strontium in the event of a breakthrough	Undiagnosed can lead to sudden death. Ruby-Fill when used according to the label serves as a diagnostic imaging aid with minimal risk. Otherwise more invasive tests.
Risk Management	• Presence of radioactive Strontium breakthrough into the administered dose. The risk is managed by: • Strontium alert and expiration levels. Improved testing for possible breakthrough	Improved testing for possible Strontium breakthrough compared to the RLD

1. Background

Product Information

Ruby-Fill is a Rubidium 82 generator that provides the drug product Rubidium 82. Rubidium decays in 75 seconds to inert Krypton gas and is promptly infused into a patient for cardiac perfusion imaging using Positron Emission Tomography. The system consists of generator containing the parent element Strontium 82 (Sr82) and a computerized drug delivery system that delivers a solution of the Rubidium (Rb82) in sterile (Calcium free) 0.9% saline; referred to in this review and label as the eluate. [redacted] (b) (4) saline from a standard source is passed through the generator to dissolve Rubidium 82 as Strontium 82, the parent, decays; the eluate is then monitored for radioactivity in the infusing sytem and then immediately administered to the imaging patient. The generator contains 85-115 mCi of Sr82 at calibration time prior to the generator's release for clinical use. figure 1 shows a schematic of the generator and elution system

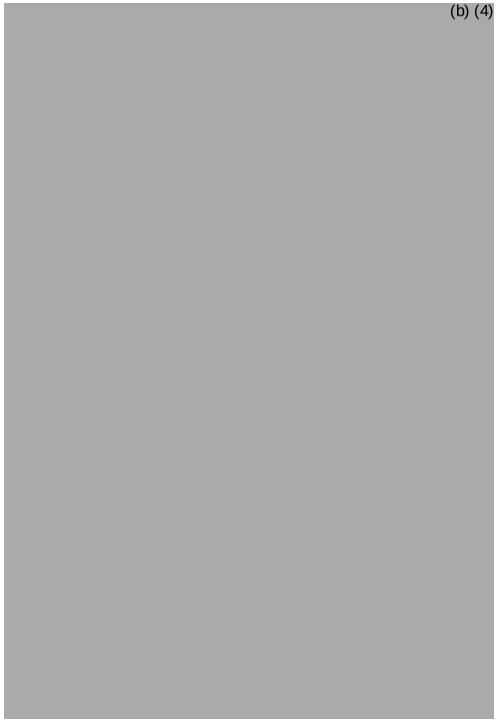

Figure 1: Ruby-Fill Schematic

Therapeutic context

Ruby-Fill is intended to aide in the diagnosis of coronary artery disease. The PET images produced following its administration show areas of possible coronary artery disease which potentially could be treated with a variety of modalities. The intended population is adults, primarily out patients, with clinical risk factors and/or symptoms of coronary artery disease.

Regulatory History

Ruby-Fill, NDA 202-153, received a complete response to its first cycle review on December, 18, 2014. The Complete Response letter outlined multiple deficiencies identified in the CMC, microbiologic, and electronic aspects of the NDA;

these deficiencies were summarized in 22 major questions/comments to the sponsor. This CDTL document encapsulates the second review cycle during which the sponsor provided specific responses to the 22 questions/comments and developed remedies such as additional studies to rectify the deficiencies identified in the Complete Response letter.

This is the second review cycle. N202-153 was filed as an ANDA with Office of Generic Drugs (OGD) on June 18, 2010 and transferred to DMIP as a 505(b)(2) NDA on September 17, 2014. During the review in OGD, CDRH was consulted for various design and electronic issues. Due to the novelty of the generator and its computerized controls, the reviews took an extensive time period. Concerns were raised about its comparability to CardioGen (N019-414), the reference listed drug (RLD). Following an internal review, OGD determined that critical differences in design and conditions of use were present compared to CardioGen and the application was transferred to DMIP.

DMIP led the subsequent review which concluded with the identification of multiple deficiencies primarily related to CMC, microbiologic and electronic issues. A CR letter issued on December 18, 2014 which catalogued the deficiencies and provided recommendations for remedies. The sponsor submitted a revision on December 30, 2015 for this review with an action date of June 30, 2016. The review was extended 90 days to September 30, 2016 due to a major amendment for further microbiological engress testing.
Foreign Use: The Ruby-Fill generator with a different infusion system has been in limted use as part of clinical trials in Canada and Switzerland.

2. Product Quality

(b) (4)

(b) (4)

Figure 2:

I concur with the conclusions of Dr. Russell that the sponsor provide adequate data to support approval.
Following their resubmission, the sponsor engaged in a dialogue with the CMC staff via IR letters and TCONs to address the deficiencies identified in the CR letter of December 18, 2014.
Below is summary of the resolution of these deficiencies (numbering from the CR letter):

Deficiency #3: Post approval (b) (4) testing
Resolution: (b) (4)

[redacted] (b) (4)

Deficiency # 4: Ruby elution system instructions for use (IFU) document [redacted] (b) (4)
Resolution: Recommended edits made to the IFU document. [redacted] (b) (4)

Deficiency #18b: Particulate Matter. Review of this issue is contained in Appendix 1 of Dr. Russell's review. The particulate matter meets specifications of USP <788>.

CMC issues identified during the review

Ability of the generator to produce the entire labeled dose range:
The sponsor proposed extending the dose range of 30-60 mCi from the RLD to 10-60 mCi.

Provision of a low dose of Rubidium 82
Recent clinical publications suggested that doses below those in the RLD label might be adequate and spare low weight patients unnecessary radiation exposure. During the review cycle the sponsor requested that doses below the RLD recommendations be added to the Ruby-Fill label; the lowest dose being 10 mCi. This request for low dosing was extensively investigated by Ann Marie Russell, the CMC reviewer, and I agree with her conclusions. The labeling implications for this dosing was reviewed by Dr. Fedowitz (section 11).
The review investigation centered around the ability of the generator to accurately provide doses in the 10 mCi range particularly the concern that a "fully [Strontium 82] loaded" generator early in its life cycle could produce a low dose at a volume that could be administered to the patient. CMC also questioned Strontium breakthrough detectability in these low doses.
Resolution: The sponsor provided clinical simulation testing that demonstrates that the generator performs within the sponsor's 10% acceptance criteria for dose error for the for total administered doses of [redacted] (b) (4) mCi of Rubidium 82. This span of Rubidium 82 radioactive content would generally be sufficient for the final proposed labeled dosing range for likely patients (0.27-0.81 mCi/kg).

[redacted] (b) (4) See Figure 2 above.

Summary Statement from Ann Marie Russell, the CMC reviewer (Executive Summary, page 21):

"The average dose error in [redacted] (b) (4) ranged from 2-3%, in [redacted] (b) (4) they ranged from 2-4% and in [redacted] they ranged from 2-3%. Additionally, all of the individual measured dose errors met the Ruby RbES system requirement specifications (± 10%) and were well within the U.S. Nuclear Regulatory Commission (*i.e. NRC)* limits for Dose Accuracy of Diagnostic Radiopharmaceuticals (± 20%)".

Provision of a 60 mCi Rubidium 82 dose

The CMC reviewers noted that based on the additional data provided by the sponsor, the generator could not provide the upper limit dose of 60 mCi as the generator advanced in age towards expiration.

Resolution: The inability to provide a large dose has significant clinical implications since a patient requiring such a dose might be schedule for a scan only to arrive at the imaging and told it could not be performed. If performed with a lower dose in a heavy patient, the resultant images might be unintereptable. The sponsor provided the graph in figure 3 which demonstrates the maximum dose that can be delivered as a function of generator age. In view of this finding, labeling has been revised to inform the clinician of the maximum dose available over the generator's lifecycle. Additionally, the installed software will reject a dosing order if the generator cannot provide that dose on a given day in its life cycle. The instructions for use manual has been significantly revised to inform the operator of the availability of a selected weight based dose.

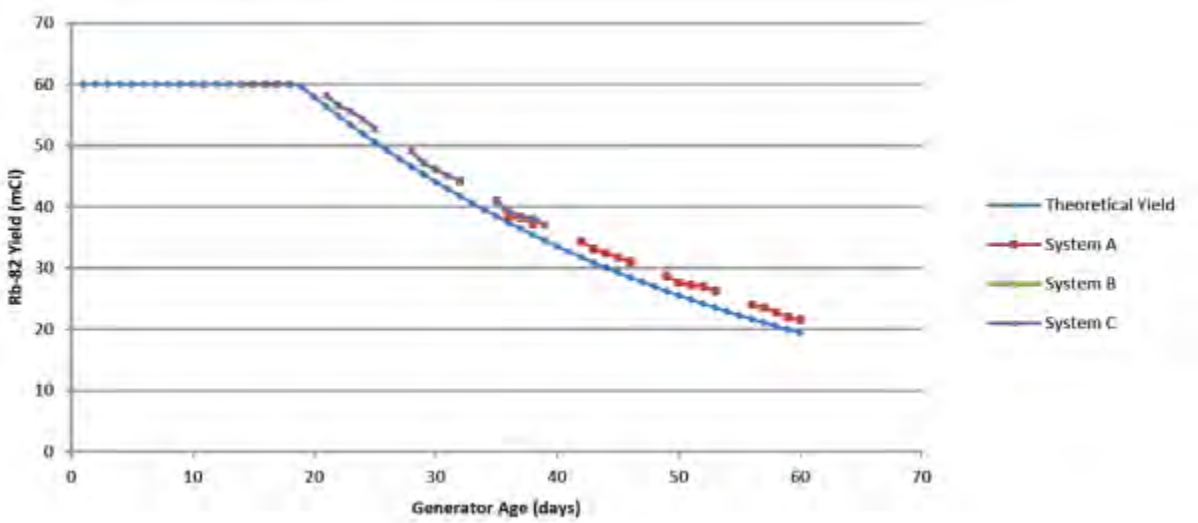

Figure 3: RUBY RbES (Effusion System) Performance (i.e. available dose) According to Generator Age – Three systems tested

Strontium breakthrough measurement at low Rubidium 82 dose:
Resolution: The sponsor explained that the breakthrough is determined by the daily calibration which uses a standard dose of 35 ml and depends on the amount of Rubidium 82 delivered by the generator in the calibration dose – not a specific patient dose.

CDRH Review
I concur with the CDRH recommendation for approval in the review by Robert Meyer. CDRH provided an analysis of the following deficiencies:

Deficiency #6: Hazard analysis and safety requirments
Resolution: The sponsor provided acceptable Fault Tree Analyses (FTA) and Design Failure Mode and Effect Analyses.

Deficiency #7: System performance and reliability – software issues
Resolution: The sponsor identified the delivery mode specifications which are acceptable and verified adequately.

Deficiency #8: Performance, reliability and safety of mechanical components of the system
Resolution: The sponsor provided an acceptable Traceability Matrix.

Deficiency #9: (CDRH aspect) (b) (4)
Resolution: (b) (4)
there is no evidence of degradation by radiation. The sponsor also provided adequate information regarding functionality and biocompatibility.

Deficiency #10: Waste management
Resolution: The daily waste is far less than the waste container 1 Liter volume. It would take several days of operator error for an overflow.

Deficiency #11: Risk assessment of residual drug in the administration lines
Resolution: (b) (4)
The minimum time between patient procedures is 10 minutes and Rubidium 82 has a half life of 75 seconds. Due to this short half life, CDRH considered the risk of residual drug exposure as acceptable.

Deficiency #12: Documentation (b) (4)
Resolution: (b) (4) Ruby-Fill passed all of the (b) (4) tests.

Deficiency #13: Risk assessment of air within the infusion system
Resolution: (b) (4)
CDRH noted (b) (4) but this is no clinical concern since Rubidium 82 is administered intravenously and air would be trapped in the lung. Air bubbles are safely introduced intravenously for some echocardiogram studies.

Deficiency #14: Verified and validated software
Resolution: Software consultant, Joseph Jorgens III, reviewed the software and deemed it acceptable.

Deficiency #15: Review of off-the-shelf (OTS) software

Resolution: Software consultant, Joseph Jorgens III, reviewed the software and deemed it acceptable.

Deficiency #16: Electrical safety and electromagnetic compatibility
Resolution: Ruby-Fill was tested for compliance with appropriate electrical standards and deemed approval.

Deficiency #18: (CDRH aspect) Risk assessment of the device-related residuals
Resolution: See Deficiency 9 and 11.

3. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology data was provided with this submission and none is necessary since the drug Rubidium 82 has already been in clinical use for over 20 years.

4. Clinical Pharmacology

Clinical pharmacology supplied a review supporting the weight-based dosing recommendation.

5. Clinical Microbiology

The microbiology reviewed focused on the potential for organisms to migrate from the patient [redacted] (b) (4) and such egress could potentially infect subsequent patients. I agree with the conclusions reached by Drs. Jessica Cole and Yeissa Chabrier Rosello that the sponsor has provided adequate information and studies to demonstrate that the Microbiological safety of the elution system is acceptable.

Deficiency #5: Mitigation of contamination [redacted] (b) (4)
Resolution: The sponsor provided details [redacted] (b) (4)

Deficiency #9: Data demonstrating that 60 days will degrade microbiologic safety.
Resolution: Clinical simulation testing: "The results show that through the duration of the system's shelf-life, the drug product remains sterile and meets the acceptance criterion for endotoxin limit."

Deficiency #17: Sterility for the disposable components of the Ruby Elution System.
Resolution: The firm provided package labeling detailing the sterilization process (b) (4)

Deficiency #19: Concern about the risk of disease transmission occurring from cross contamination (b) (4)

Resolution:
The sponsor agreed to perform another dye ingress study simulating conditions of use as specified by the microbiology reviewers.

From the microbiology review page 19:

(b) (4)

See Figure 4.

Figure 4: Simulation testing for dye egress. (b) (4)

Overall Microbiology Conclusion

The microbiology reviews found the test results acceptable and recommended approval.

6. Clinical/Statistical- Efficacy

The submission does not include any new efficacy data and none are needed because the performance characteristics of Rubidium 82 PET are well known.

7. Safety

The major safety issue based on previous experience with CardioGen is the potential for excess Strontium 82 and Strontium 85 to enter the administered eluate . Strontium 82 with a half-life of 25 days is the parent of Rubidium and Strontium 85 (half-life 65 days) is also contained in the generator. As noted previously in this review, the main theoretical concern is bone marrow toxicity from these bone seeking, long lived radioactive Strontium isotopes. Ruby-Fill has a computerized system to perform daily tests for Strontium in the eluate. Once an "Alert" level is reached indicating an increased, but still acceptable level of Strontium in the eluate, repeat Strontium testing is then performed after every 4 patients. If the Strontium level on this repetitive testing reaches (b) (4) the generator has reached expiration and removed from clinical service. Additionally, expiration can also be reached after 30 liters of flows through the generator or after 60 days of use. Exceeding these volume and time parameters may in themselves lead to Strontium "breakthrough". The Ruby-Fill computerized system will not allow dosing to occur if these parameters are exceded.

Safety Update
The sponsor provided updated safety information. Ruby-Fill has not been in routine clinical use outside of the United States. There have been some clinical trial use in Switzerland and Canada. In Canada, Ruby-Fill has been used in the ARMI (Alternative Radiopharmaceutical for Myocardial Imaging) and other smaller clinical studies. The sponsor reports one case in 2011 of Strontium "breakthrough" in which the patient did receive unintended radiation exposure. Investigation of the case reveal that the Ruby-Fill generator had undetected manufacturing deficiencies which were not a systemic issues.

Other CR questions related to Safety

I concur with the DMEPA reviewers that the sponsor provided an adequate Human Factors study and training program.

Deficiency #1 Inadequate data reporting in the Human Factors Study
Resolution: The sponsor provided additional data from study participants at all the sites where the study was performed. With this additional data. DMEPA concluded the Human Factors Study was acceptable and demonstrated that Ruby-Fill could be used properly by trained nuclear medicine technicians

Deficiency#2 Provision of a training program
Resolution: The sponsor provided detailed plans for a training/re-training program; DMEPA concluded that the plans were adequate.

8. Advisory Committee Meeting

No advisory committee is needed since Rubidium 82 is not a new molecular entity.

9. Pediatrics

No pediatric plan was needed because of the initial date of the submission and none was provided. The application does not trigger PREA and no pediatric study is
planned.

10. Other Relevant Regulatory Issues

There are no outstanding relevant regulatory issues.

11. Labeling

Updated labeling
I concur with the review and recommendations by Dr. Fedowitz.

Prescribing Information

Dosing and Administration

The labeling review centered on determining an optimal dosing regimen based on the data provided by the sponsor concerning the minimum and maximal doses the generator could provide over its life cycle. Additionally the sponsor provided publications which indicated that advances in PET imaging equipment allowed for the administration of lower doses than originally recommended by the sponsor and in the CardioGen label.

The sponsor provided dosing recommendations based on the guidelines from various academic organizations. FDA responded by requested supporting data to justify their recommendation . The sponsor replied in SD 44 by providing 36 peer reviewed publications in which various doses of Rubidium 82 were utilized. The submission was extensively

reviewed by Dr. Fedowitz, the DMIP Associate Director for Labeling. Twelve studies used weight based dosing (3-10 MBq/kg) with a mid-range of activity of 24 mCi and a range of 16-32 mCi. There were 16 additional studies using weight-based dosing where the MBq/kg was not provided. In these studies the mean activity was 44.4 mCi with a lower bound in the range of 20 mCi. Eight studies used fixed dosing with a mid-range activity of ~44 mCi and a lower bound in the range of 15 mCi. The most relevant publication cited by the sponsor was the ARMI study (Kaster, et. al. J Nucl Cariol. 2012 Dec 19(6): 1135-45) in which a small subgroup of patients underwent cardiac catheterization:
From Dr. Fedowitz's review.
"The authors used weight based dosing (10 MBq/kg) in approximately 1500 patients to a develop normal database (77 patient studies) to be used for quantification of myocardial perfusion and diagnosis of CAD using low-dose Rb 82 and 3D EPT CT imaging. In addition, 45 patients who had angiography and PET CT were used to evaluate the accuracy of the database using automated analysis (SSS)." Table 1 provides dosing infomation from the study

Dosing Regimen	Mid-range Activity	Range
10 MBq/kg	~25 mCi	9.7-56 mCi

Table 1: Dosing information from the ARMI study

The sponsor provided updated dosing recommendations (b) (4)

(b) (4)

FDA Dosing Recommendations
The review team concluded that the data provided demonstrated that weight based dosing was already in extensive clinical use with doses below the RLD recommendation and the ARMI study in conjunction with the other studies provided adequate supportive data for the sponsor's dosing recommendation.
Since imaging technology rapidly changes and varies with imaging center, (b) (4) the clinician is provided with an extensive dosing range. Differing from the RLD, the label has a weight based dosing recommendation – MBq/kg or mCi/kg – where the lowest dose the generator can produce supported by

sponsor CMC data is 10 mCi. Except for very low weight patients, most patients would receive doses in the 20 to 30 mCi range which is in the range found in more recent publications provided by the sponsor.

From the draft label with FDA edits accepted by the sponsor:

"The recommended weight-based dose of rubidium Rb 82 is between 10-30 Megabecquerels (MBq/kg)/kg [0.27-0.81 millicuries mCi/kg]"

Accuracy of Dosing

The label also notes that the measurement of the radiation dose is accurate within ±10%, a standard set by the sponsor. Using the computerized system, the clinician may put in the patient's weight; with a previously selected MBq/kg (or mCi/kg) from the label, the computer will calculate the dose for the patient.
To alert clinicians to dosing limitations with an aging generator, the label contains a table showing the maximum dose the generator can deliver over its life span.

Boxed Warning, Warnings & Precautions

The Boxed Warning was maintained as with CardioGen because Strontium breakthrough is a fundamental concern with Rubidium 82 generators. Ruby-Fill has safeguards to avoid excess Strontium in the eluate so the "Alert" level parameters which were arbitrarily chosen for CardioGen are less stringent than for Ruby-Fill. Ruby-Fill can accommodate a large volume of saline throughput in the generator and has a longer half-life.

Parameter	CardioGen (RLD)	Ruby-Fill
Alert Limits		
Sr 82 microCi/mCi Rb 82	0.002	0.004
Sr 85 microCi/mCi Rb 82	0.02	0.04
Volume (Liters)	14	20

Expiration Limits		
Sr 82 microCi/mCi Rb 82	0.01	0.01
Sr 85 microCi/mCi Rb 82	0.1	0.1
Volume (Liters)	17	30
Days	42	60

Table 2: Comparison of Alert and Expiration Parameters for CardioGen and Ruby-Fill

The Instruction for Use document was similarily revised to reflect the changes noted in the labeling.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There are no REMS for Ruby-Fill

Postmarketing Requirements (PMRs) and Commitments (PMCs)

None are needed.

13. Recommended Comments to the Applicant

The CDTL recommends approval.

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/s/

IRA P KREFTING
09/29/2016

LIBERO L MARZELLA
09/29/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	12/11/2014
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	202153
Applicant Name	Jubilant Draximage
Date of Submission	June 18, 2010
PDUFA Goal Date	10/11/2014
Proprietary Name **Established (USAN) Name**	Ruby-Fill Rubidium Rb82 Chloride for Injection
Dosage Form **Strength**	Sterile solution for injection The generator contains (b) (4) Sr82. (b) (4) generator delivers a single dose of NMT 60mCi and (b) (4) a maximum volume of 60mL per infusion (b) (4)
Indications	for assessing regional myocardial perfusion (b) (4)
Regulatory Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Clinical	Ira Krefting MD
CMC	David Place PhD, Milagros Salazar PhD, and Eldon Leutzinger PhD
OGD/Microbiology	Dupeh Palmer PhD
OGD/DLRS	Shimer Martin
DMEPA	Michelle Rutledge PharmD, Yelena Maslov Pharm D
CDRH/GHDB	Ryan McGowan and Alan Stevens
CDRH/DRH	Andrew Kang MD
CDRH	Quynh Nhu Nguyen PhD

OND - Office of New Drugs
ONDQA - Office of New Drug Quality Assessment
CMC - Chemistry Manufacturing and Controls
DMEPA - Division of Medication Error Prevention and Analysis
OGD - Office of Generic Drugs
DLRS - Division of Legal and Regulatory Support

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CDRH - Center for Devices and Radiological Health
DRH - Division of Radiological Health
DAGRID - Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
GHDB - General Hospital Devices Branch

1. Introduction

This review summarizes my assessment of the approvability of this application under section 505(b)(2) of the statute.

Product

Ruby-Fill is a Strontium 82/Rubidium 82 (Sr82/Rb82) generator and drug infusion and delivery system that provides an eluted solution of the drug substance Rubidium Rb82 Chloride in sterile 0.9% saline. The generator contains (b) (4) mCi of Sr82 at calibration time.

The complete system is composed of a saline bag (b) (4) Rb-82 generator column, (b) (4) and radiation calibrator system. The radionuclide generator contains Sr82 chloride adsorbed onto hydrous (b) (4) stannic oxide packed in a column. The generator is regulated as a drug while the drug product delivery system is regulated as a device.

Rb82 decays by positron emission with a half-life of 1.3 minutes to stable krypton gas. Due the short Rb82 half-life, the generator with its drug infusion system is designed to deliver promptly an injection of the Rubidium82 eluate. The drug product is proposed for use for cardiac perfusion imaging using Positron Emission Tomography (PET).

Regulatory History

The manufacturer, Jubilant Draximage, submitted this marketing application on June 18, 2010 to the Office of Generic Drugs (OGD) as an abbreviated new drug application (ANDA). The drug product is Ruby-Fill a Sr82/Rb82 generator and drug infusion and delivery system. The Applicant referenced as the listed drug CardioGen-82 a Sr82/Rb82 generator containing 90-150 mCi of Sr 82 and marketed by Bracco Diagnostics under NDA 019414. The reference listed drug was approved in 1989.

The final product is Rubidium Chloride Rb 82 Injection USP solution administered to a patient by infusion. The product (b) (4) contains the active ingredient, rubidium chloride (b) (4) and the inactive ingredient 0.9% sodium chloride.

OGD's Division of Legal and Regulatory Support (Shimer Martin) determined on November 16, 2012 that the application was not eligible for submission under 505(j) because the proposed conditions of use of Ruby-Fill are not the same as those

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of the RLD due to differences in the rates of infusion ((b) (4) ml/min vs. 50 ml/min) and total volumes (maximum of 60 ml vs. 100 ml) of the drug product. The OND CMC reviewer (Dr. Leutzinger) in a December 12, 2012 memorandum underscored the importance of this difference. The potential for medication error exists if the incorrect rate of infusion specified for a Cardiogen-82 generator were used for the Ruby-Fill generator.

As a result of this finding, the applicant submitted on January 17, 2013 a request for conversion of ANDA 202153 to NDA 202153 under the 505(b)(2) regulations. On January 15, 2013 OGD confirmed that the Office would continue to review the application using its authority to approve 505(b)(2) applications. Finally on September 17, 2014 OGD informed the applicant that DMIP would take the lead in the review of the NDA.

2. Chemistry Manufacturing and Controls

The Ruby-Fill elution system is diagrammed below. (b) (4)

(b) (4)

Product Quality

I concur with the assessment by the CMC reviewer Dr. Place that the level of post–approval testing proposed [redacted] is inadequate. This is a critical deficiency [redacted]

[redacted]

The CMC reviewer determined that product complies with the USP monograph for the Rubidium 82 generator. [redacted] The generator is eluted with additive–free 0.9% sodium chloride for injection (USP). [redacted] $Sr82Cl_2$ is the precursor radionuclide. It is sourced from [redacted] The CMC reviewer Dr. Salazar reviewed the manufacturing processes under DMF [redacted] and found them to be adequate.

Device Components

I concur with the assessment by the GHDB reviewers Drs. McGowan and Stevens (see May 5, 2014 review) that critical deficiencies in the application with regard to the elution system preclude an assessment of the safety and efficacy of the system.

The infusion system consists of [redacted] The elution system's physical layout and system integration are designed for real-time error detection and process monitoring. [redacted]

The elution system is provided with all the components necessary for use, including an onboard dose calibrator and a computer. The unit is on wheels for positioning near the PET camera in close proximity to the patient receiving the infusion of drug.

The consultants' evaluation called attention to the need for requirements and specifications of the infusion system, performance testing and risk analysis and software analysis. Serious deficiencies also included the lack of verification of compliance with sterility, biocompatibility and electrical safety and electromagnetic compatibility standards.

Microbiological Quality

I concur by the assessment on May 27, 2011 by the FDA microbiology reviewer Dr. Palmer that the applicant has demonstrated an adequate level of sterility assurance for the manufacturing process of the generator.

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3. Nonclinical Pharmacology and Toxicology

The applicant did not include nonclinical studies and this submission does not require additional nonclinical data.

4. Clinical Pharmacology and Biopharmaceutics

There is no new clinical pharmacology information in this NDA and none is needed.

5. Clinical Microbiology

This section is not applicable to this NDA.

6. Clinical/Statistical Efficacy

The submission does not include any new efficacy data and none are needed because the Rb82 Cl drug products are identical.

7. Safety

One critical safety issue with Sr82/Rb82 generators is the potential for breakthrough of Sr82 and Sr85. For this reason daily testing of the generator eluate is needed and expiry of generator is defined by level of Sr82 (0.01 microCi/mCi rb82) and Sr 85 (0.1 microCi /mCi Rb 82) breakthrough. The breakthrough limits are the same as those for Ruby-Fill and the RLD and are acceptable. Other expiry criteria for time post calibration date or total eluate volume (respectively 60 days and 30 L for Ruby-Fill).

Human Factors Studies

I concur with the FDA reviewers' findings that these deficiencies of human factors studies prevent the verification of the adequacy of the human factor testing and are grounds for a complete response action.

The FDA human factors specialist Quynh Nhu Nguyen on May 29, 2014 completed a consultative review of the human factor validation study and usability risk analysis report provided by the Applicant. The reviewer determined that the study report was materially incomplete and identified concerns with the methodology used in the studies. The FDA primary clinical reviewer (Dr. Krefting) independently reviewed the study reports and agreed with the consultant on the key deficiencies in the study reports.

Dr. Krefting identified the following specific deficiencies that need to be addressed.

- The protocols for the studies titled: “Ruby Rb-82 Elution System Usability Risk Analysis” (10/17/2013) and “Ruby Rubidium Elution System Summative Usability Validation Report” (1/28/2014) were not provided.
- Data from a testing site (Brigham and Women’s and Cardiac Imaging Associates) were not provided.
- It is not clear if a separate training manual or the general user manual was used for the testing and if mitigation strategies have been adopted and retesting performed.

Break-through testing validation

I concur with the FDA reviewer finding on May 29, 2014 that the generator breakthrough testing procedure is acceptable.

Dr. Andrew Kang performed a consultative review of the validation study to assess the accuracy of the break-through testing of the generator. Break-through testing is a critical product quality control procedure that the user is required to perform daily. The testing is designed to assess the level of Strontium 82 and 85 activity in the Rubidium 82 eluate and is one of the determinants of generator expiry.

8. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

9. Pediatrics

No pediatric plan was needed because of the initial date of the submission and none was provided. The application does not trigger PREA and no pediatric study is planned.

10. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis

I concur with the assessment by the DMEPA reviewer (Dr. Rutledge) on April 1, 2014 that the proposed proprietary name Ruby-Fill is acceptable. Dr. Rutledge’s assessment is consistent with previous review conducted by DMEPA on December 16, 2010.

Review of the product labeling has been deferred. We have asked DMEPA to evaluate the potential for medication errors and recommend mitigation strategies that might be needed for the use of CardioGen-82 and Ruby-Fill in the same clinical facility. Both final products consist of radioactive Rubidium for use in cardiac imaging. However, the two rubidium generators differ in the volumes and flow rates of the injected infusion into the patient.

Office of Compliance

The Office of Compliance performed an inspection of the facility for manufacturing, packaging and labeling of commercial batches of Rubidium generator at Jubilant Draximage and issues an "acceptable" decision on January 16, 2014. The OC also inspected the following facilities: (b) (4) Each facility was determined to be acceptable and the overall recommendation by the Office on May 1, 2014 was "acceptable".

Labeling Review

The manufacturer has revised the labeling on OGD's advice. Dr Krefting review describes a number of differences between the use of the Ruby-Fill and the RLD that raise the potential of medication errors. This issue remains under review.

I concur with Dr. Krefting's assessment that the lack of adequate information in the application regarding the training program for the users is a major deficiency. Training requirements and training packages should be finalized prior to marketing.

Complete review of the labeling is deferred until the deficiencies in the application are addressed.

11. Decision/Risk Benefit Assessment

I agree with the assessments by the clinical and human factors specialist reviewers, the CMC reviewers, and the GHDB reviewers that serious deficiencies in the marketing application preclude an assessment of the safety and efficacy of Ruby-Fill.

DMIP communicated to the applicant the outstanding deficiencies in the NDA in teleconferences held on December 12 and 17, 2014. The applicant will need to address the outstanding issues for Ruby-Fill related to human factor studies, training program for the users and a testing program for post-approval (b) (4) Data on the overall system performance and reliability, electrical safety and electromagnetic compatibility, biocompatibility and infection control are needed. Validation of the system software is also necessary.

Given these deficiencies a complete response action will be taken.

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/s/

LIBERO L MARZELLA
12/18/2014

Date: 11/28/14

Division of Medical Imaging Products

Clinical Review

Ruby-Fill

NDA 202-153

Reviewer: Ira Krefting, M.D.

Background

Ruby Fill is a "bed-side" drug production system to produce rubidium 82 (Rb 82), a radioactive drug administered during nuclear cardiac testing to aid in the identification of coronary artery disease by outlining regions of decrease myocardial perfusion. Ruby Fill consists of a Rb 82 generator column containing radioactive strontium (Sr 82), the parent of Rb 82, and an administration cart with computerized functions for direct administration of Rb 82 to the cardiac imaging patient. Rb 82 mimics Potassium which is metabolically active in cardiac muscle and extracted by the myocardium proportionally to blood flow; therefore Rubidium 82's radioactive emissions provide images of functioning/ nonfunctioning cardiac muscle and coronary blood flow. Ruby Fill is similar to CardioGen, a rubidium generator that has been on the market for over 20 years, but differs from CardioGen in generator design and Rb 82 dose administration parameters.

The main safety concern inherent to Rubidium generators is leaching of radioactive Strontium isotopes from the generator column into the elution which is then injected into a patient. Rubidium 82 has a half-life of 75 seconds, the Strontium isotopes have longer half-lives and expose the patient to unnecessary additional radiation. Rubidium generators should be designed and labeling instructions provided, to insure that the radioactive isotopes of Strontium in the patient infusion is below the USP standards: The activity level of Sr 82 should not be more than 0.02 microCi per mCi of Rb 82 and Sr 85 is not more than 0.2 microCi per mCi of Rb 82 (USP Monographs: Rubidium Chloride Rb 82 Injection). For example, the Strontium level expiration limits for CardioGen were set at: 0.01 microCi/ mCi of Rb 82 for Sr 82 and 0.1 microCi/ mCi Rb 82 for Sr 85 (both half of the USP limits).

Regulatory History

The application was received on June 18, 2010 and was initially managed by OGD since Ruby-Fill was considered a generic product with CardioGen being the reference listed drug (RLD). Upon further review, differences in design and administration rates were identified and led to the application being reclassified as a 505(b)(2). In view of this designation and DMIP's familiarity with CardioGen, the application was transferred to DMIP for further review and regulatory action.

Clinical Data

No clinical data was provided in the application and none is needed. The supportive clinical studies cited in the Clinical Studies section (section 14) of the proposed Ruby Fill label are the same studies cited in the existing CardioGen label. The literature citations provided in the original Ruby Fill application date from the early 1990's and relate to the general development of a rubidium generator.

CMC Review

Dr. David Place reviewed the design of the Ruby-Fill generator column that contains Strontium 82. A pure saline solution (no Calcium should be present) is passed through the column to capture Rb 82 which is the daughter of the radioactive decay of Strontium 82. Rubidium 82 undergoes further decay to Krypton, an inert gas, which is expelled from the lungs. Dr. Place found no deficiencies with the column design. (b) (4) Elution of the Ruby-Fill generator in a manner consistent with clinical usage (item G, Dr. Place's review) did not reveal any Strontium in the elution until day (b) (4) of generator elution and then the Strontium was at a minimal level below concerns for Strontium "breakthrough" (Strontium in the elution beyond the USP or product defined limit).

Dr. Place did identify a critical concern: The post-approval testing is inadequate. The sponsor plans to (b) (4) Dr. Place recommends that (b) (4) (item H, Dr. Place's review).

Human Factors

The human factors study should demonstrate that representative operators can use the manual – Instructions for Use (IFU) effectively. To evaluate the adequacy of the human factors study, DMIP reviewed the following sponsor provided reports:

Ruby Rb-82 Elution System Usability Risk Analysis (10/17/2013)
Ruby Rubidium Elution System Summative Usability Validation Report (1/28/2014)

Rb-82 Elution System Hazard Analysis (4/28/2011)

In general the sponsor followed the guidance titled: “Applying Human Factors and Usability Engineering to Optimize Medical Device Design“ for performing a human factors study and presenting the results. As recommended in the guidance likely users, in this case nuclear technologists, performed the testing procedures on a standard Ruby-Fill production line generator in simulation mode. This scenario adequately reproduced the clinical experience and allowed for the identification of any safety issues in the operation of Ruby-Fill. The performance of the technologists was observed; coaching was only done when failure to perform a specific task would impede the rest of the testing procedure (such as difficulty with use of the “on” switch). The participants also rated the quality of the instruction manual. The sponsor did not provide all the detailed testing results from the participants, precluding FDA’s ability to adequately review the study. From the limited information available for review, no major safety issues were identified.

CDRH also performed a review of the human factors studied and identified several methodological deficiencies such as concerns about the background training of the technologists and coaching. These concerns were reconciled in a dialogue between DMIP and CDRH; For example; DMIP deemed it acceptable for participating technologist not to have experience with CardioGen; the testing could be done in small cohorts of 2 technologists at a time; and limited coaching was acceptable as noted above.

DMIP identified the following critical concerns upon reviewing the human factor study reports submitted by the sponsor:

1. The protocols for the listed studies were not provided to FDA.
2. The detailed results were not provided to FDA from subjects at the Brigham and Women’s and Cardiac Imaging Associates sites participating in the study reported in the “Ruby Rubidium Elution System Summative Usability Validation Report”.
3. From the provided data, DMIP cannot discern whether a separate training manual or the user manual provided to FDA was the basis of operational learning for the subjects who participated in the studies.
4. Regarding the “Ruby Rb-82 Elution System Usability Risk Analysis”: DMIP cannot discern which mitigation strategies (such as responses to computer inputing errors) have been instituted and whether additional testing has been performed to confirm their efficacy.

Label Review

The supplied label generally parallels the CardioGen label and has been updated through subsequent submissions as modifications have taken place to the CardioGen label. This labeling review section highlights the differences between Ruby-Fill and CardioGen; this section should not be construed as a complete labeling review. Comparisons with CardioGen are solely for illustrative purposes.

The Ruby Fill label states that the infusion system automatically checks the dose for the level of Rb 82 and contaminants of Sr 82 and Sr 85; for CardioGen these functions require dose manipulations and hand calculations by the user. Below is a comparison of the Ruby-Fill labeled submitted on 9/23/2013 (CTD Module I -1.14.1.3 Package Insert) to the CardioGen label approved on 2/08/2012.

- Boxed Warning:

  a. The Ruby Fill alert levels (when additional Sr testing should be done) for Sr 82 and Sr 85 are double those of CardioGen. *Reviewer's Note: The CardioGen Alert Limit was set by the sponsor* (b) (4) *for the presence Sr 82 and Sr 85 in the administered dose (see Background section. Subsequent "stress" testing of CardioGen generators demonstrated that these Alert Limits were appropriate to ensure product quality.*

  b. When the alert levels are reached for Ruby Fill, repeat breakthrough testing is performed after every 4 patients instead of 750 ml for CardioGen. *Reviewer's Note: For Ruby Fill, after the alert limit was reached, repetitive testing would take place* (b) (4) *--see section 2.2 b below. "After every 4 patients" is vague and does not account for the potential of small dose volumes. Final labeling should contain a repetitive testing interval determined by a specific elution volume metric in mL).*

  c. The volume expiration limit is 30 L compared to 17 L for CardioGen.

  d. The time expiration limit is 60 days compared to 42 for CardioGen.

  e. The expiration levels of Sr 82 and Sr 85 are identical for Ruby Fill and CardioGen.

Section 2 Dosage and Administration

- **2.2 Rubidium Rb 82 Chloride Injection Dosage:**

  a. Ruby-fill is to be eluted at a rate of (b) (4) mL/minute; for CardioGen the rate is 50 ml/min.

  b. For Ruby Fill the maximum administered volume is 60 ml and a cumulative volume (rest/stress) of 120 ml; for CardioGen the maximum administered volume is 100 mL and a cumulative volume (rest/stress) of 200 mL. *(Reviewer's Note: With both Ruby Fill and CardioGen the same amount of Rb 82 is delivered over the same time period. Only the volume of the infusion varies.)*

- **2.4 Directions for Eluting Rubidium Rb 82 Chloride Injection**

  a. Discard the first 75 mL each day; for CardioGen discard 50 mL

- **2.5 Eluate Testing Protocol**

  a. The Ruby Fill label states: (b) (4) *Reviewer's Note:* (b) (4) *The user manual provides details on the actual operation of the Ruby Fill generator (see below).*

  b. For Ruby Fill 75 mL of Sodium Chloride Injection is to be flushed automatically; the CardioGen label states 50 mL.

  c. For Ruby Fill the generator recharge is "approximately 15.2 minutes"; for CardioGen it is 10 minutes.

  d. After step 7, the label states: " (b) (4) Table 1 to calculate the decay factor for Rb-82; step 4 (above). *Reviewer's Note: The label probably is referring to "R" which is described in step 3 & 5. The calculations seem to be made automatically anyway.*

- **3 Dosage Forms and Strengths**

  a. Ruby Fill has (b) (4) millicuries of Sr-82 at calibration time; CardioGen has 90-150.

- **16 How Supplied/Storage and Handling**

a. The Ruby-Fill generator is encased in a lead shield; CardioGen is encased in a lead shield surrounded by a labeled plastic container.

b. The Ruby-Fill generator should be stored at [redacted] C ([redacted] F); CardioGen is to be stored at 20-25° C (68-77° F)

Conclusions of the Labeling Review

The Ruby Fill label generally follows both the format and details of the CardioGen label; the Rb 82 dose administered to the patient is the same with either generator. [redacted] Ruby-Fill is [redacted] contained in a smaller volume (60 mL –Ruby-Fill versus 100 mL CardioGen). The Ruby-Fill label is generally clear and indicates that most preparatory steps will be performed automatically by the onboard computer.

User Manual

User Manual version 4.5 was reviewed.

The manual is aimed at the technologist and provides basic information about the system and details about operating the system and quality controls. [redacted]

[redacted]

For illustration, graphical user interfaces (GUI) taken from the provided manual are shown below.

Figure 1: Display before starting a patient

Figure 1: Patient set up with infusion options

Conclusions of the Manual Review

The instructions appear succinct and easy to follow. (*See the Human Factors section for further details on the expectations for a manual – Instructions for Use- IFU document.)* The recommendations for the user manual reflect general observations:

- The table of contents should have a page number adjoining each listed item for quick reference. An index would also be helpful.
- A section on responding to critical, serious emergencies would be helpful.
- The manual contains several typographical errors, lacks clear page numbering and text overrunning images – a final edition will require further editing.
- It is unclear whether this particular version of the manual has been validated for use by representative, potential operators.

Training

This reviewer was unable to identify a "Training Manual" in the submissions from the sponsor. This review is based on the information quoted from the User Manual version 4.5:

(b) (4)

The draft guidance containing training recommendations for training with devices (cited above) has the following advice that is relevant to Ruby-Fill:

"Training requirements and training packages should be finalized prior to clinical use of the device, whether that use occurs with the IDE submission or following FDA clearance".

Conclusion of the Review of the Training Provision

- No information is presented to judge the adequacy of this program, its effectiveness, and need for retraining. The sponsor has not fulfilled the recommendations of the draft guidance.
- The training program could parallel the voluntary program instituted by the CardioGen sponsor.

- The sponsor should develop a program to monitor the use of the generators and confirm the safe use by the clinical sites. Unless adverse reactions or irregularities are identified in generator use, reporting can be on a routine basis consistent with NDA safety reporting requirements.

Regulatory Action

Rub-Fill is Rb 82 generator undergoing review through the 505 (b)(2) pathway. This review has identified deficiencies that need to be addressed. For this reason I recommend a CR action. A complete review of the package insert will be deferred until all the CMC, manual and training issues are addressed.

Below are the specific deficiencies to be addressed by the sponsor:

1. CMC- The post-approval testing is inadequate. As recommended by Dr. Place, the sponsor should provide an adequate post-approval (b) (4) program.

2. Regarding the incomplete information in the Human Factors Studies. The following requests are made:

    a. Provide the protocols for the human factor studies.

    b. Detailed results from subjects participating in the Ruby Rb-82 Elution System Usability Risk Analysis at the Brigham and Women's and the Cardiac Imaging Associates sites are missing. Provide the details results in the same format as the results from the Hartford site.

    c. For the deficiencies (such as computer input errors) identified in the "Ruby Rb-82 Elution System Usability Risk Analysis" provide the mitigation strategies and the results of testing that supports the utility of the proposed mitigation stategies

3. Regarding the Training Program- Provide specific proposals for a training program and a methodology to document its effectiveness. Training requirements and training packages should be finalized prior to clinical use.

4. Regarding the User Manual- Provide a final version of an Instructions for Use (IFU) document which is structured with a table of contents, index, page numbering and a section on responding to serious patient emergencies involving Ruby-Fill administration.

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/s/

IRA P KREFTING
12/09/2014

LIBERO L MARZELLA
12/11/2014
I concur with Dr. Krefting's assessment and recommended regulatory action

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CHEMISTRY REVIEW(S)

Chemistry, Manufacturing and Controls (CMC) Labeling Memo – User Manual

NDA 202-153

Ruby-Fill® (Rubidium Rb 82 Generator)

Jubilant DraxImage, Inc.

by
Chemistry Reviewer: Anne Marie Russell, Ph.D.
Office of New Drug Products
Division of New Drug Products 2 (Branch VI)
for
Division of Medical Imaging Products (DMIP)

Reference ID: 3991705
486 of 1085

1. NDA 202-153

2. Labeling Memo – "The Ruby Rubidium Elution System User Manual"

3. REVIEW DATE: 20-Sept-2016

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date (Panorama)
Chemistry Review #2 Complete Response (Anne Marie Russell Ph.D., CMC reviewer)	20-SEP-2016

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Receipt Date	DARRTS SDN	Contents
Quality amendment	12-Sep-2016	email	Response to Information Request #3 – volume expiry (30L)
Quality amendment	25-Sep-2016	email	Response to User Manual Information Request

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	16751 Trans-Canada Highway Kirkland, Quebec Canada H9H 4J4
Representative:	Susan P. Spooner, Ph.D. INC Research, LLC, 4800 Falls of Neuse Road Suite 600 Raleigh, NC 27609 phone 919-745-2492
Telephone:	(514) 630–7087

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby-Fill® [1]
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2).

The reference listed drug (RLD) is Cardiogen 82 (N019414)

10. PHARMACOL. CATEGORY: Cardiac Positron Emission Tomography

[1] The Ruby-fill ^{82}Rb generator is operated by the Ruby-Fill® Elution System (RbES) [redacted] (b) (4)

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY/PACKAGING: Variable strength eluent (mCi/mL) depending on generator release activity level, generator age, elution system operation mode and time between elutions. Column is loaded with (b) (4) ^{82}SrCl at calibration (adsorbed onto SnO_2). Dose is 10 – 60 mCi ^{82}Rb.

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: ^{82}RbCl
Molecular Weight: 117.5 daltons

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs: none.
B. Other Documents: none.

Chemistry Memo

Ruby Rubidium Elution System User Manual

In CMC Review #2 (Complete Response), two open issues (D1 and D2 below) with the User Manual were still under negotiation with the Applicant at the time of document completion, so this follow-up memo reviews the User Manual and documents the outcome.

(b) (4)

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Evaluation: Acceptable

Overall Evaluation of the User Manual: Acceptable as revised.

E. Label - PI (Prescribing Information)
This CMC reviewer provided input to the following sections of the PI throughout labeling negotiations with the Applicant: Highlights, Section 2.4 Elution System, Section 2.6 (b) (4) Eluate Testing Protocol, 2.8 RUBY-FILL Dose Delivery Limit, Section 3 Dosage Forms and Strengths, Section 11 Description and Section 16 How Supplied and Storage/Handling. Negotiations with the Applicant were ongoing when this memo was finalized - see approval letter for the final version of the PI

Signatures:
Primary Reviewer
Anne Marie Russell, Ph.D. CMC reviewer, ONDP, Division II, Branch VI

Secondary Reviewer:
Danae Christodoulou, Ph.D. Acting Branch Chief, ONDP, Division II, Branch VI

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

/s/

ANNE M RUSSELL
09/28/2016

DANAE D CHRISTODOULOU
09/28/2016

NDA 202153
Resubmission

OPQ N202153 Integrated Quality Assessment

Review Date: 09/23/2016

Drug Name/Dosage Form	Rubyfill[R] Rubidium Rb 82 Generator/Intravenous Infusion
Strength	(b) (4) not to exceed a total of 60 mL
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Jubilant DraxImage Inc. (JDI), 16751 Trans-Canada Highway, Kirkland, Quebec, Canada H9H 414
US agent, if applicable	Susan P. Spooner, Ph.D., INC Research, LLC (4800 Falls of Neuse Road, Suite 600, Raleigh, NC 27609; phone 919-745-2492)

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505(b)(2) – RLD is Cardiogen-82 (NDA 19414)**

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. DMFs:

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	REVIEWER
(b) (4)	II		(b) (4)	3	01/17/2012 (adequate)	Milagros Salazar, Ph.D.
	II			3	01/18/2012 (adequate)	Milagros Salazar, Ph.D.

[1]The DMF
[2]Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3]Reviewed previously and no revision since last review

B. Other Documents: *IND, RLD, or sister applications*
N/A

3. **CONSULTS:**

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
CDRH			Robert Meyer, MS

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Drug Product	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Process	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Microbiology	Yeissa ChabrierRosello, Ph.D.	OPQ/OPF/Microbiology
Facility	Michael Klapal	OPQ/OPF/DBP/BI
Biopharmaceuticals	N/A	N/A
Project Manager (R.Ph.)	Thao Vu, R.Ph.	OMPT/CDE/OPQ/OPRO/DPMI/RBPMBI
Application Technical Lead	Eldon E. Leutzinger, Ph.D.	ONDP/Branch VI/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment (EA)	N/A	N/A

Table 2 Documents Reviewed

DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
Complete Response (Resubmission-Class 2)	12/30/2015	Submission in response to Complete Response Letter	Anne Marie Russell, Ph.D., ONDP/Branch VII/Division II
Quality amendments	06/01/2016 O6/29/2016 08/30/2016 09/12/2016	Response to IR's	Anne Marie Russell, Ph.D., ONDP/Branch VII/Division II

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202153 for Rubyfill is recommended for approval, from the standpoint of Chemistry, Manufacturing and Controls, pending conclusions by the CDRH review (not yet final as of the date of this Integrated Executive Summary). Both Microbiology and Manufacturing Facilities are recommending approval.

1. Summary of Complete Response issues & Subsequent IR's, Facilities

ISSUE		STATUS
CMC From Complete Clinical Response Letter (12/18/2016)	Deficiency #3 – (1) clinical use simulation and (2) post approval testing protocol (b) (4) Deficiency #4 – clarification of Rubyfill Elution System Instructions	**Resolved** – clinical use simulation found acceptable. Post-approval testing protocol (b) (4) acceptable. Clarifications of Elution System instructions acceptable – response of 06/01/2016
CMC	CMC IR of 5/13/2016 – (b) (4)	**Resolved** – (b) (4) post-

(Continue from Complete Response Issues)	[redacted] (b) (4)	approval stability protocol resolved **Resolved** – [redacted] (b) (4) stability testing – response of 06/01/2016

ISSUE		STATUS
CMC (uncertainty in 10 – 60 mCi dose)	CMC IR of 05/16/2016 – (1) assessment of uncertainty in the dose (10 – 60 mCi) at the maximum and (2) minimum range of the system operation (flow rates, ^{82}Rb concentration, elution volume).	**Resolved** - issues (1) and (2) – response of 06/01/2016
CMC (new low dose limit of 10 mCi)	CMC IR of 5/16/2016 – (1) capability of dose calibrator to detect new alert limits (0.004 µCi ^{82}Sr/mCi ^{82}Rb, 0.04 µCi ^{85}Sr/mCi ^{82}Rb) in the new dose of 10 mCi, (2) DL for strontium and assessment of uncertainty of measurement at lowest level (~ 0.01 µCi), (3) calculations to determine the reported capability, (4) study reports (data, analysis) referenced in document "RUBY-FILLRubidum Rb 82 Generators.	**Resolved** – issues (1), (2), (3) and (4) – response of 06/01/2016
CMC (System Performance; Capability of Delivering Patient Dose)	CMC IR of 5/16/2016 – (1) assessment of delivered dose volume, strength and rate of delivery over lifetime of generator (release, mid-life, expiry) for minimum (10 mCi) and maximum (60 mCi). (2) assessment of uncertainty of values in (1) basis of assessment. (3) Rationale for [redacted] (b) (4) delivery rate proposed in label	**Resolved** - issues (1) and (2) – response of 06/01/2016. **Resolved** – issue (3) - response of 09/12/2016
Microbiology	Lack of dye ingress validation (1) testing [redacted] (b) (4) and (2) the limitations of the dye ingress test to simulate possible microbial ingress into the system	**Resolved** – issues (1) and (2) – responses of 8/17/2016

ISSUE		STATUS
Biopharm	N/A	N/A
Facilities	**^{82}Sr** – manufacture (b) (4) & established manufacturer of ^{82}Sr. **Drug Product** (*Jubilant Draximage* – drug manufacturer, *Jubilant Hollisterstier* – release & stability tester, (b) (4) – release & stability tester. (b) (4) – release & stability tester	**Resolved** (b) (4) – Corrections involving validation of test methods for ^{82}Sr completed (b) (4) acceptable by profile **Facilities in manufacture of drug product found acceptable on basis of profile and inspectional history**
CDRH	Review of the Dose Delivery System involves several aspects, ranging from software to the physical system (b) (4) From the standpoint of those issues involving the physical system, the only mechanical issue that remained after review in CDRH (b) (4)	**Conclusions on this issue, software and any other issues are pending as of the date of this integrated executive summary**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None

II. Summary of Quality Assessments

INTRODUCTION:

The product from Rubyfill (Rubidium Rb 82 Generator) is ^{82}RbCl in saline, without excipients. It is produced in a "radionuclide generator" with the long/short-lived radionuclide pair (^{82}Sr/^{82}Rb). Due to the short physical half-life of ^{82}Rb (75 seconds), ^{82}RbCl is administered directly to a patient through an infusion delivery system connected to the generator. Based on the governing principles of a radionuclide generator, $^{82}Sr^{2+}$ is expected to remain stationary on a short chromatography column of hydrous stannic oxide, allowing for $^{82}Rb^{+}$ to elute from the column, thus effecting separation of $^{82}Rb^{+}$ from $^{82}Sr^{2+}$ (parent radionuclide). Hydrous stannic oxide is the stationary phase ("matrix"), whereas 0.9% Sodium Chloride (USP) is the mobile phase.

A. Drug Substance [USAN Name] Quality Summary

Chemically, the drug substance is **^{82}RbCl** and the USAN is Rubidium Chloride Rb 82. Rubidium (Rb) is Element 37 belonging to Group 1 of the Periodic Table, commonly referred to as the alkali metals, with electronic configuration of $[Kr]5s^1$. By virtue of the very large size of the 2nd ionization potential, Rb ion exists solely in the +1 oxidation state, and the chemistry of Rb and all

its isotopes is that of Rb^+. Rubidium possesses 32 isotopes, of which only 2 are naturally occurring (^{85}Rb, 72.2% natural abundance; ^{87}Rb, 27.8% natural abundance and radioactive with long physical half-life of 4.9 x 10^{10} years). The remaining isotopes, including ^{82}Rb, are radioactive and are not found in nature. The product of the decay of ^{82}Rb is stable Kr [$^{82(37+45)}_{37}Rb \rightarrow {}^{82(36+46)}_{36}Kr + \beta^+ + \nu$], in which a proton is converted to a neutron [$p^+ \rightarrow n + \beta^+ + \nu$ (neutrino)], resulting in a change in Z from 37 to 36. In this process, two particles (β^+ and ν) carry away the energy of the nuclear transition, and the energy spectrum of the positrons is a continuous distribution, as opposed to a emission of a discrete energy peak. Once β^+ particles are formed, they have a finite, but very short lifetime. On collision with electrons, the β^+ particles annihilate forming two 511 KeV γ-rays at approximately 180^0 apart, the basis of PET imaging with ^{82}Rb.

^{82}Rb is obtained from ^{82}Sr, and the overall process characterizing the nuclear transformations is as follows: $^{82(38+44)}_{38}Sr \rightarrow {}^{82(37+45)}_{37}Rb \rightarrow {}^{82(36+46)}_{36}Kr + \beta^+ + \nu$. ^{82}Sr (absorbed as $^{82}Sr^{2+}$ to the column matrix) decays by orbital electron capture (EC) in which the **nucleus absorbs one of the atom's orbital electrons, reacting with a proton, neutralizing it with formation of a neutron and a neutrino** [$e^- + p^+ \rightarrow n + \nu$ (neutrino)]. Overall, there is a change in Z from 38 to 36. This is seen in the Periodic Table, with ^{82}Sr going from Group 2 to ^{82}Rb in Group 1, then wrapping around (left-wise) in the Periodic Table to stable ^{82}Kr of the Inert Gasses (Group 18).

The conversion of ^{82}Sr to ^{82}Rb occurs on the generator column [$^{82}Sr \rightarrow {}^{82}Rb + \nu$], since the ^{82}Sr (as $^{82}Sr^{2+}$) stays put (in principle), although some relatively small amounts of $^{82}Sr^{2+}$ leaks out, by virtue of the imperfect chemistry of absorption to stannic oxide matrix.

QUALITY SUMMARY **– the radionuclidic identity of the drug substance (due to ^{82}Rb) is defined by well-established physics ($^{82}Sr \rightarrow {}^{82}Rb + \nu$), and radiochemical identity ($^{82}RbCl$) by the exchange process that occurs on the generator column matrix** (b) (4) **releasing $^{82}Rb^+$ (with Cl^-) with elution by saline. There are no radionuclide impurities arising from the nuclear transformation itself. The only issue pertinent to the quality of the $^{82}RbCl$ is that of** (b) (4)

B. Drug Product [Established Name] Quality Summary

Rubyfill [Rubidum Rb 82 Generator]. The generator eluate (containing $^{82}RbCl$) is administered directly to patients, and has a stand-alone indication (*PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease*). Hence, **by 21 CFR 310.3(n), Rubyfill (Rubidium Rb 82 Generator) is considered a drug, and furthermore defined as a PET drug and regulated under 21 CFR 212**. All of the CMC information pertaining to the generator, its manufacture and controls is in the NDA.

Rubyfill (Rubidium Rb 82 Generator) is a radionuclide generator that contains (b) (4) $^{82}SrCl_2$ adsorbed onto hydrous (b) (4) stannic oxide in a column (b) (4) The System front view and Schematic owing the internal network of functional parts is reproduced from the NDA, as follows:

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(b) (4)

Dose of ^{82}RbCl to Patient

(b) (4)

(b) (4) JDI is proposing to extend the dose range to 10 – 60 mCi, introducing a **new low dose limit of 10 mCi**.

- **New Low Dose (10 mCi)**

Several issues arose regarding this new dose limit, namely (IR, 5/13/2016) affecting risk to the patient, namely (a) uncertainty of the dose delivered, and (b) uncertainty in the detectability of strontium breakthrough.

ISSUE – **New Low Dose #1 (5/13/2016)** – IR #1 - **assessment of uncertainty in the in dose range (10 – 60 mCi)** – **RESOLVED**. (b) (4)

(b) (4)

ISSUE – **New Low Dose #2** (5/13/2016) – IR #1 - **limit of detection** – **RESOLVED**. The limit of detection of the dose calibrator is determined (b) (4)

(b) (4)

Summaries of Rubyfill elution system performance testing is provided.

- **System Performance**

The clinical team (DMIP) had requested an explanation of the slower maximum infusion rate (30 mL/min). That for Cardiogen-82 is 50 mL/min.

ISSUE – **System Performance** (5/13/2016) – IR #2 – absence of demonstrated **capability of the Rubyfill system to deliver minimum and maximum dose (10 mCi and 60 mCi) at the beginning of generator life to its expiration, test method and controls** - **RESOLVED**. In a tcon with JDI (7/13/2016), additional data was requested. Data was provided by Draximage (b) (4)

(b) (4)

ISSUE – **System Performance** (9/06/2016) – IR #3 – absence of **data use to support proposed Rubyfill labeled elution volume of 30 L at expiry** – **RESOLVED**. Data provided (9/12/2016) are not primary stability data, because of differences between test conditions and commercial operation, and between development and commercial generators. As a consequence, these data are of a secondary nature. Yet, it is pertinent that at the 30 L expiry point, the release acceptance criteria were not exceeded. Some data from Canadian generators (b) (4) were provided. These generators were operated to simulate clinical use, although not using the commercial elution system. The impact of differences do not adversely affect the breakthrough performance (shown by JDI). The data from the Canadian generators is primary and supportive of the 30 L expiry. The sum total of all the data assures that breakthrough performance of the commercial generators will be met at 30 L expiry. **In light of these considerations, it is to be noted that the stability data provided does not include data from 3 commercial generators operated with the commercial elution system and with commercial** (b) (4) **Hence, the post-approval stability program will be very important in confirming the expected performance of the commercial product.**

Microbiology

After the initial review (06/03/2016) and responses to address multiple deficiencies, the issues that remained were (1) lack if dye ingress validation testing (b) (4) and (2) the limitations of the dye ingress test to simulate possible microbial ingress into the system. Based on the information to address the issues in (1), their results demonstrate that the risk of cross-contamination (b) (4) is well controlled by the safeguards put in place (b) (4) Regards (2), the firm's response is twofold. (b) (4)

These assessments and rationale were deemed to be acceptable by the microbiologist

reviewer (Yeissa ChabrierRossello, Ph.D.) for a final determination that all microbiology deficiencies identified in the application are resolved.

Dose Delivery System

Review of the Dose Delivery System involves several aspects, ranging from software to the physical system (b) (4) From the standpoint of those issues involving the physical system, the only mechanical issue that remained after review in CDRH (Robert Meyer, M.S). (b) (4)
The final review conclusion on this issue, including an assessment by DMIP, and of the software and any other issues is pending as of the date of this integrated executive summary.

Rubyfill User Manual

(b) (4)

(b) (4)

These issues relating to improvements in the User Manual are currently under negotiation with JDI.

Labeling

Some final labeling changes (Michele Fedowitz, M.D., DMIP; Anne Marie Russell, Ph.D., ONDP) are proposed to the Outer Label (main label, assay label) and will be communicated to JDI. There are no other outstanding labeling issues, other than the continuing negotiations with JDI on the User Manual.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Rubyfill
Non Proprietary Name of the Drug Product	Rubidium Rb 82 Generator
Non Proprietary Name of the Drug Substance	Rubidium Chloride Rb 82 (USAN)
Proposed Indication(s) including Intended Patient Population	Imaging of the myocardium under rest or pharmacologic stress in patients with suspected or existing coronary artery disease
Duration of Treatment	N/A
Maximum Daily Dose	60 mCi
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations
N/A

E. Novel Approaches
N/A

F. Any Special Product Quality Labeling Recommendations
None

G. Process/Facility Quality Summary (see Attachment A)
See I.A. Recommendations and Conclusion on Approvability (Summary of Complete Response Issues & Subsequent IT's, Facilities)

H. Life Cycle Knowledge Information (see Attachment B)
N/A

Risk Assessment - Drug Product (Rubidium Rb 82 Generator)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation[6]**	**Lifecycle Considerations/ Comments****
Radionuclidic Identity/purity	(b) (4)		N/A	(b) (4)	N/A
Radiochemical identity			N/A		N/A
Radiochemical purity			N/A		N/A
Chemical Purity			N/A		N/A
Strength (mCi/mL)			Data provided to address		N/A
pH			N/A		N/A
Stability			N/A		N/A

Microbiology		(b) (4)	Information to resolve deficiencies	(b) (4)	N/A

1. Radionuclidic Identity/Purity – sources of ^{82}Sr (b) (4) previously reviewed under DMF's, and determined to be acceptable for use in the rubidium generator.
2. Radiochemical Identity/Purity – established in (b) (4) DMF's.
3. Chemical Purity – Trace Metals – established in (b) (4) DMF's.
4. Microbiology – see Microbiology Review (Yeissa ChabrierRosello, Ph.D.); RPN (after modification when applicable) x S x D.
5. Overall Risk Assessment, (b) (4) (low, based on resolution of all issues for CMC & Microbiology).

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Chemistry, Manufacturing and Controls (CMC)
Review of Complete Response
Drug Product

NDA 202-153

Ruby-Fill® (Rubidium Rb 82 Generator)

Jubilant DraxImage, Inc.

by
Chemistry Reviewer: Anne Marie Russell, Ph.D.
Office of New Drug Products
Division of New Drug Products 2 (Branch VI)
for
Division of Medical Imaging Products (DMIP)

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-153
2. REVIEW #2 (Complete Response)
3. REVIEW DATE: 11-MAY-2016
4. REVIEWER: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS:

Document	Document Date (DARRTS)
Chemistry Review #1 (David Place Ph.D., CMC reviewer)	19-SEP-2014
CMC memo #1 (David Place Ph.D., CMC reviewer)	11-Dec-2014
CMC memo #2 (David Place Ph.D., CMC reviewer)	11-Dec-2014
FDA action letter (Complete Response (CR))	18-Dec-2014

History of the application: This is the second review cycle. N202-153 was originally filed in 2006 as an ANDA and was converted to NDA (505b2) due to clinical differences from the Reference Listed Drug (Cardiogen N019414). The original NDA 505b2 application was not approved. See CR letter, issued 18-Dec-2014.

Review Clock: The original PDUFA date for this Complete Response was 30-Jun-2016. On 29-Jun-2016, the review clock was extended to 30-Sep-2016 due to receipt of a major amendment (CDRH).

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Receipt Date	DARRTS SDN	Contents
Complete Response (Resubmission Class 2)	30-Dec-2015	30	Complete response to CR letter.
Quality Amendment	01-Jun-2016	36	Response to Information Request #1
Quality Amendment	29-Jun-2016	43	Response to Information Request #2
Quality Amendment	30-Aug-2016	47	Response to Information Request #2 – clinical simulation test
Quality amendment	12-Sep-2016	email	Response to Information Request #3 – volume expiry (30L)

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	16751 Trans-Canada Highway Kirkland, Quebec Canada H9H 4J4
Representative:	Susan P. Spooner, Ph.D. INC Research, LLC, 4800 Falls of Neuse Road Suite 600 Raleigh, NC 27609 phone 919-745-2492
Telephone:	(514) 630–7087

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby-Fill® [1]
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2).

The reference listed drug (RLD) is Cardiogen 82 (N019414)

10. PHARMACOL. CATEGORY: Cardiac Positron Emission Tomography

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY/PACKAGING: Variable strength eluent (mCi/mL) depending on generator release activity level, generator age, elution system operation mode and time between elutions. Column is loaded with (b) (4) ^{82}SrCl at calibration (adsorbed onto SnO_2). Dose is 10 – 60 mCi ^{82}Rb.

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: ^{82}RbCl
Molecular Weight: 117.5 daltons

[1] The Ruby-fill ^{82}Rb generator is operated by the Ruby-Fill® Elution System (RbES) (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A. DMFs have been reviewed in previous review cycles. No new DMFs in this submission.

B. **Other Documents:** none.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Facility Inspection	NA		
Pharm/Tox	NA		
Biopharm	NA		
Labeling Nomenclature Committee	NA		
Methods Validation	NA		
DMEPA			
Environmental Assessment	NA		
Microbiology	acceptable	15-Sept-2016	Yeissa Chabrier-Roselló, Ph.D.
CDRH	pending		Robert Meyer. M.S.

Chemistry Review for NDA 202-153 Complete Response

I. Recommendations

A. Recommendation and Conclusion on Approvability:
From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval, pending acceptable findings by the CDRH review, which is not yet final as of this writing. The proposed volume expiry (30L) and time expiry (60 days) for the generator is granted, when operated using the commercial elution system [redacted] (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Review of Applicant's Response to CMC Deficiencies:

Two CMC deficiencies were identified in the 18-Dec-2014 Complete Response letter to the Applicant under the heading PRODUCT QUALITY items #3 and #4.

The format of this review is as follows: the deficiency from the Complete Response letter is in normal font, *the Applicant's response provided in this submission is in italics* and **the reviewer's evaluation is in bold font**.

Deficiency #3

[redacted] (b) (4)

Applicant's response (received 30-Dec-2015):
In this Complete Response submission, the Applicant provided a revised post-approval stability protocol [redacted] (b) (4)

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III. Additional issues which arose during review:

Background: This reviewer compiled Table A which compares Cardiogen generator (RLD) with the Ruby-fill proposed commercial generator:

Table A Rubidium-82 generator: Comparison to RLD		
Characteristic	Cardiogen generator (RLD)	Ruby-Fill generator
Dose	30 – 60 mCi Rb 82	10 – 60 mCi Rb 82
Flow rate	50 mL/min	15 – 30 mL/min
Elution volume per dose	< 100 mL	< 60 mL
Elution time per dose	Not specified	(b) (4)
Radioactivity delivered by generator*		
• at calibration (Day 0/ 1.00)	90 – 150 mCi Rb 82	85 – 115 mCi Rb 82
• at first clinical use (Day 11/ 0.737)	(b) (4) mCi Rb 82	(b) (4) mCi Rb 82
• at end of expiry^	(b) (4) mCi Rb 82 (^Day 42/ 0.312)	(b) (4) mCi Rb 82 (^Day 60/ 0.189)
How dose is delivered	User manually operates Cardiogen system control panel	User input to Ruby-fill system software interface, software controls infusion.
Operation modes	(b) (4)	
Expiry - time	42 days	60 days
Expiry - volume	17L of eluent	30 L of eluent
Calibration dose	N/A	35mL at 20 mL/min

*Calculated from fraction remaining in Table 6 Cardiogen 82 and Ruby-fill labels

A. New low dose (10mCi):

During the review cycle, Jubilant DraxImage (JDI) proposed to extend the dose range (b) (4) to 10 – 60 mCi, which introduced a new low dose limit (10mCi). The review issues from a CMC standpoint for the new low dose are two fold – the risk to the patient regarding uncertainty in the dose administered and the detectability of strontium breakthrough.

Dose uncertainty: Any measurement has an inherent uncertainty due to the limitation of the equipment and the measuring method. (b) (4) The Complete Response submission and the original NDA submission did not provide an assessment of the uncertainty of these radioactivity measurements – see comment below.

Strontium breakthrough detectability: The levels of strontium (^{82}Sr and ^{85}Sr) in the patient dose are monitored daily in the calibration dose eluted during the Daily Quality Control (Section 7 in the User Manual). The eluent is allowed to decay out the ^{82}Rb and the residual radioactivity is measured by the dose calibrator. The system then calculates the levels of strontium using the measured residual radioactivity, equations and limits specified in the Ruby-fill label. It is unknown if the strontium breakthrough alert limit (^{82}Sr 0.004 per µCi/mCi of ^{82}Rb,

^{85}Sr 0.04 per µCi/mCi of ^{82}Rb) in the new low dose (10 mCi) is below the detectability limit of the system. An evaluation of the Limit of Detection (LOD) of strontium breakthrough in the system is needed - see comment below.

The following three comments were sent to the Applicant on 13-May-2016 in CMC Information Request #1, response received 1-Jun-2016:

1. **Provide an assessment of the uncertainty in the dose (10 – 60 mCi) administered to the patient at the maximum and minimum range of the system operation (e.g. flow rates, ^{82}Rb concentration, elution volume/time). Explain the basis for each assessment. Tabulate the data where possible.**

Response: Applicant provided dose error data from Clinical Simulation Test 4 (Protocol ##3000069-P/ Appendix 8-2 Clinical Simulation Study Report). (b) (4)

(b) (4)

Dose Range	Flow-Rate	Average Dose Error
(b) (4)		

Table 6

(b) (4)

Review:

(b) (4)

(b) (4)

Table B
Dose Accuracy in Clinical Simulation Test 4

Dose (mCi)	Flow rate (mL/min)	Dose Error (%)		
		avg	min	max

(b) (4)

(b) (4)

(b) (4)

[redacted]

As per Michele Fedowitz, M.D., clinical reviewer, (via email on 8-June-2016) the dose error is not clinically significant and is acceptable.

Evaluation: Acceptable

2. **Limit of detection for strontium in new low dose (10 mCi):**
   a. **Discuss the capability of the dose calibrator to detect strontium at alert levels (^{82}Sr 0.004 per µCi/mCi, ^{85}Sr 0.04 per µCi/mCi) in the new low dose of 10mCi. Include an assessment of the limit of detection (LOD) for strontium using the supplied dose calibrator unit and the uncertainty in that dose calibrator measurement** (b) (4) **Provide calculations used to determine the reported capability.**

   Response: The Applicant explained that breakthrough levels are reported as the amount of strontium per the amount rubidium (e.g. ^{82}Sr 0.004 µCi/mCi ^{82}Rb and ^{85}Sr 0.04 µCi/mCi ^{82}Rb) and are assessed during the daily calibration of the system. (b) (4) [redacted]

   Per the recently submitted report (RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing), the Limit of Detection (LOD) of the dose calibrator is experimentally determined (b) (4) [redacted]

(b) (4)

[redacted]

Evaluation: Acceptable. (b) (4) [redacted] The alert limit is essentially at or below the limit of detection of the dose calibrator when the generator is at expiry, but not earlier. This is acceptable because of the extensive margin built into the alert limits to assure patient safety.

b. Provide the study reports (data, analysis) referenced in the document "RUBY-FILL® Rubidium Rb 82 Generators - Evaluation of Strontium Isotope Breakthrough" (Appendix 3-1) which summarized test results for:

- **i. RES.RBY.SDY.034 Volume Limits and Strontium Breakthrough**
- **ii. RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing**
- **iii. RES.RBY.SDY.042 Interim Report: Summary of RbES (b) (4) Performance Testing**
- **iv. RES.RBY.SDY.054 REPORT: Summary of Ruby-Fill Elution System Performance Testing**

v. **RES.RBY.SDY.070 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Low Usage**
vi. **RES.RBY.SDY.072 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Extreme Usage**

Response: Reports provided.
Evaluation: Acceptable. See Maximum volume at expiry (30L) in Section C below.

B. **System performance/ Flow rate of eluent:**

During label review, the clinical team requested an explanation of the slower maximum infusion rate recommended for Ruby-fill (30 mL/min) compared to the reference listed drug Cardiogen (50 mL/min). Additional data regarding infusion times and full system performance are needed to evaluate the clinical impact.

The following comment was sent on 13-May-2016 in CMC Information Request #1, response received 1-Jun-2016.

3. **For the maximum (60mCi) and minimum (10mCi) dose range, provide an assessment of the delivered volume, concentration (mCi/mL) and rate of delivery (mL/min) for the lifetime of the generator (release, mid-life and expiry). Include an assessment of the uncertainty in the values and explain the basis for each assessment. Describe the rationale for the 30 mL/min maximum rate proposed in the draft label. Tabulate the information, where possible.**

Response: Data provided for minimum, intermediate and maximum dose at generator release, mid-point and expiry, in Tables 11, 12 and 13 below.

Time Point	Dose (mCi)	Volume (mL)	Flow-Rate (mL/min)	Elution Time (sec)
(b) (4)				

(b) (4)

The maximum flow of the Ruby-Fill system is 30 mL/min (b) (4)

Initial Evaluation: Not Acceptable. (b) (4) Data were not provided for a minimum dose (10 mCi) delivered from a generator at release and for a maximum dose (60mCi) delivered from a generator at mid-point and expiry. These conditions represent the limits of the system. (b) (4)

(b) (4)

(b) (4)

[redacted]

The following deficiency was sent to the Applicant on 20-Jun-2016 in CMC Information Request #3:

CMC Deficiency: (b) (4) [redacted]

Information needed to resolve the deficiency:

1. **Provide data to demonstrate that the commercial system is capable of delivering the maximum and minimum dose (10mCi and 60mCi) at the beginning and end of generator lifetime within the proposed operating range of the system** (b) (4) [redacted] **Include raw data, averages, n value, uncertainty and range of values (minimum and maximum).**

   First Response: received 29-Jun-2016 (SDN #43):
   No new clinical simulation test data provided. (b) (4) [redacted]

(b) (4)

Initial evaluation: Not acceptable. In this response, JDI summarized previously submitted clinical simulation data, which had already been reviewed and found to be inadequate because data at system limits were missing. In the 13-Jul-2016 tcon, FDA advised that additional data were needed and JDI agreed to conduct additional testing and submit.

(b) (4)

Second Response: received 30-Aug-2016 (SDN #47) Clinical Simulation Study Report – Dosing Evaluation. The submitted Executive Summary is copied below:

(b) (4)

[redacted]

Final Evaluation: Acceptable. Data were provided to demonstrate that the minimum dose (10 mCi) is delivered throughout the generators' lifetime (60 days) at the minimum and maximum operating conditions (flow, time, elution volume) in all three elution modes. (b) (4)

[redacted]

(b) (4)

(b) (4)

These clinical performance results were provided to the clinical review team to assess the suitability of the clinical simulation test, who found them acceptable.

2. **Provide the test method used to produce the data and summarized descriptions of how the reported data (volumes, flow and times) are determined. Include data for dose, flow, time (infusion, elution), system mode and volume (infusion, elution, total). Briefly describe the fluid path of the system as it delivers the entire infusion to the patient, including the radioactive dose and any non-radioactive saline – for each mode of operation, if different.**

Response: received 29-Jun-2016 (SDN #43): The submission described the test method, including how reported data are determined (see summary below, Table C, compiled by this reviewer) and the method used to determine accuracy of that reported data in the dose error calculations. The fluid paths were also described in diagrams, see Appendix.

Evaluation: Acceptable. The test method and calculation of dose error are acceptable. Dose, volume and flow rate accuracy were determined against the "true" value and precision was determined from repeat (n=2) measurements.

Table C. Summary of how submitted data are determined in clinical simulation tests		
Data	System component	"True" value
(b) (4)		

*This true value is a best estimate based on use of a calibrated dose calibrator (b) (4)

3. **Describe the controls in place which prevent the system from operating when an undeliverable dose is requested by the user. This may include for example - software lockout controls, user manual instructions and labeling language.**

Response received 29-Jun-2016 (SDN #43): JDI described the software controls in place and the constraints on the deliverable dose for all parameters (Table 6 below):

Parameter	Minimal value	Maximal value
(b) (4)		

Table 6- generator activity level constraints

Evaluation: Acceptable. (b) (4)

(b) (4)

C. **Maximum volume at expiry (30L):**

The Ruby-fill label (Section 2.7), in keeping with the RLD Cardiogen label, specifies three attributes for expiry: volume (30L), time (60 days) and strontium breakthrough level (Sr 82 and Sr 85) as follows:

2.7 RUBY-FILL® Expiration

Stop use of the RUBY-FILL® Rubidium Rb 82 Generator once any one of the following Expiration Limits is reached:

- A total elution volume of 30 L has passed through the generator column, or
- Expiration date of the generator (60 days post-manufacturing), or
- An eluate Sr 82 level of 0.01 µCi/mCi (kBq/MBq) Rb 82, or
- An eluate Sr 85 level of 0.1 µCi/mCi (kBq/MBq) Rb 82

The acceptance criteria for two of these attributes, time and breakthrough level, have been found acceptable in the previous review cycle. Acceptable stability data were provided in the original submission to support the 60 day expiry (see CMC review#1 David Place, Ph.D. 19-SEP-2014). The strontium breakthrough levels are based on the (b) (4)

The third attribute, volume (30L), was not discussed in CMC review #1. In this review cycle, the report "Investigation of Volume Limits and Strontium Breakthrough" RES.RBY.SDY.034 dated April 2014 to support the expiry volume was submitted on 01-Jun-2016 in Quality Amendment (DARRTS SDN#36). Figure 2 in the report (below) provides Sr-82 breakthrough values to show that generator (b) (4) delivered 30L of doses with strontium levels below the breakthrough acceptance criteria (b) (4)

(b) (4)

Initial Evaluation: Not Acceptable. The submission provides a summary report (b) (4)

(b) (4)

The following comment was sent to the Applicant in Information Request #3 on 6-Sept-2016:

1. **Provide data to support the proposed Ruby-fill generator labeled elution volume expiry of 30L. Describe the test procedure used to collect the data and differences from the proposed commercial product (e.g. generator, elution system, operating conditions).**

Response: Received (via email) 12-Sep-2016.

The Applicant provided four pieces of information to support their proposed 30L expiry data:

1. Developmental and validation generators – stability data in original NDA (30-Jun-2010):

(b) (4)

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Response: At the time of completing this review, this User Manual issue is still under negotiation with the Applicant. See subsequent CMC labeling memo.

Final Overall Evaluation of the Application:

Pending acceptable findings by CDRH review, which is not yet final as of this writing, the NDA is recommended for approval from a CMC standpoint, with the proposed volume expiry (30L) and time expiry (60 days) when operated using the commercial elution system (b) (4)

Pertinent communications with the Applicant during the Review Cycle:

Communication type	Date sent to Applicant	CMC comments & deficiencies
tcon	11-May-2016	See minutes in DARRTS. CMC discussed dose and calibration.
CMC Information Request #1	13-May-2016	1. Post-approval stability protocol: (b) (4) [redacted] 2. Provide an assessment of the uncertainty in the dose (10 – 60 mCi) administered to the patient at the maximum and minimum range of the system operation (e.g. flow rates, ^{82}Rb concentration, elution volume/time) . Explain the basis for each assessment. Tabulate the data where possible.

N202-153 CHEMISTRY REVIEW#2

Communication type	Date sent to Applicant	CMC comments & deficiencies
		3. Limit of detection for strontium in new low dose (10 mCi): a. Discuss the capability of the dose calibrator to detect strontium at alert levels (^{82}Sr 0.004 per µCi/mCi, ^{85}Sr 0.04 per µCi/mCi) in the new low dose of 10mCi. Include an assessment of the limit of detection (LOD) for strontium using the supplied dose calibrator unit and the uncertainty in the dose calibrator measurement [redacted] (b) (4) Provide calculations used to determine the reported capability. b. Provide the study reports (data, analysis) referenced in the document "RUBY-FILL® Rubidium Rb 82 Generators - Evaluation of Strontium Isotope Breakthrough" (Appendix 3-1) which summarized test results for: i. RES.RBY.SDY.034 Volume Limits and Strontium Breakthrough ii. RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing iii. RES.RBY.SDY.042 Interim Report: Summary of RbES [redacted] (b) (4) Performance Testing iv. RES.RBY.SDY.054 REPORT: Summary of Ruby-Fill Elution System Performance Testing v. RES.RBY.SDY.070 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Low Usage vi. RES.RBY.SDY.072 REPORT: Summary of Ruby-Fill Elution System 4. For the maximum (60mCi) and minimum (10mCi) dose range, provide an assessment of the delivered volume, concentration (mCi/mL) and rate of delivery (mL/min) for the lifetime of the generator (release, mid-life and expiry). Include an assessment of the uncertainty in the values and explain the basis for each assessment. Describe the rationale for the 30 mL/min maximum rate proposed in the draft label. Tabulate the information, where possible.

Communication type	Date sent to Applicant	CMC comments & deficiencies
CMC Information Request #2	20-Jun-2016	**CMC Deficiency #1: Undeliverable dose.** System performance has not been demonstrated over the lifetime of the generator for the full range of doses (10mCi to 60mCi) within the operating range of the system, consequently some doses may not be deliverable. The data provided from Clinical Simulation Test 4 did not provide test results for 10mCi at generator release or for 60mCi at generator expiry – conditions which represent the limits of the system as labeled. Information needed to resolve the deficiency: 1. Provide data to demonstrate that the commercial system is capable of delivering the maximum and minimum dose (10mCi and 60mCi) at the beginning and end of generator lifetime within the proposed operating range of the system (b) (4) (b) (4) (b) (4) Include raw data, averages, n value, uncertainty and range of values (minimum and maximum). 2. Provide the test method used to produce the data and summarized descriptions of how the reported data (volumes, flow and times) are determined. Include data for dose, flow, time (infusion, elution), system mode and volume (infusion, elution, total). Briefly describe the fluid path of the system as it delivers the entire infusion to the patient, including the radioactive dose and any non-radioactive saline – for each mode of operation, if different. 3. Describe the controls in place which prevent the system from operating when an undeliverable dose is requested by the user. This may include for example - software lockout controls, user manual instructions and labeling language. **CMC Comment #1:** Your proposal (b) (4) in your stability protocol is not acceptable. Revise the post-approval stability protocol (b) (4) (b) (4)
tcon	23-Jun-2016	See minutes in DARRTS. CMC discussed data to support deliverable doses.
Clock Extension	29-Jun-2016	No CMC information was sent. The clinical division informed the Applicant "On June 15, 2016, we received your June 11, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee

Communication type	Date sent to Applicant	CMC comments & deficiencies
		goal date is September 30, 2016."
Tcon	13-Jul-2016	See minutes in DARRTS. CMC discussed data to support deliverable doses.
Information Request #3	6-Sept-2016	Provide data to support the proposed Ruby-fill generator labeled elution volume expiry of 30L. Describe the test procedure used to collect the data and differences from the proposed commercial product (e.g. generator, elution system, operating conditions)."
Information Request #4 (joint with clinical)	15-Sept-2016	We are concerned that your user manual does not clearly explain (b) (4) [redacted] (b) (4) [redacted]

IV. Labeling:

Labeling is ongoing by the review team at this time. See CMC labeling memo.

V. Overall recommendation: The application, as amended, is recommended for approval pending acceptable review by CDRH.

VI. Signatures:

CMC primary reviewer: Anne Marie Russell, Ph.D. I recommend approval (pending acceptable CDRH review).

CMC secondary reviewer: Danae Christodoulou, Ph.D. Branch Chief. I concur.

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Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 9/22/2016 02:58:25PM
GUID: 5050dd27000012a4c69bfc70b47660b7

Anne Russell

Digitally signed by Anne Russell
Date: 9/22/2016 02:56:53PM
GUID: 508da7210002a03c7e3cba5e276a8027

Facility -1

ASSESSMENT OF THE FACILITIES

(b) (4)

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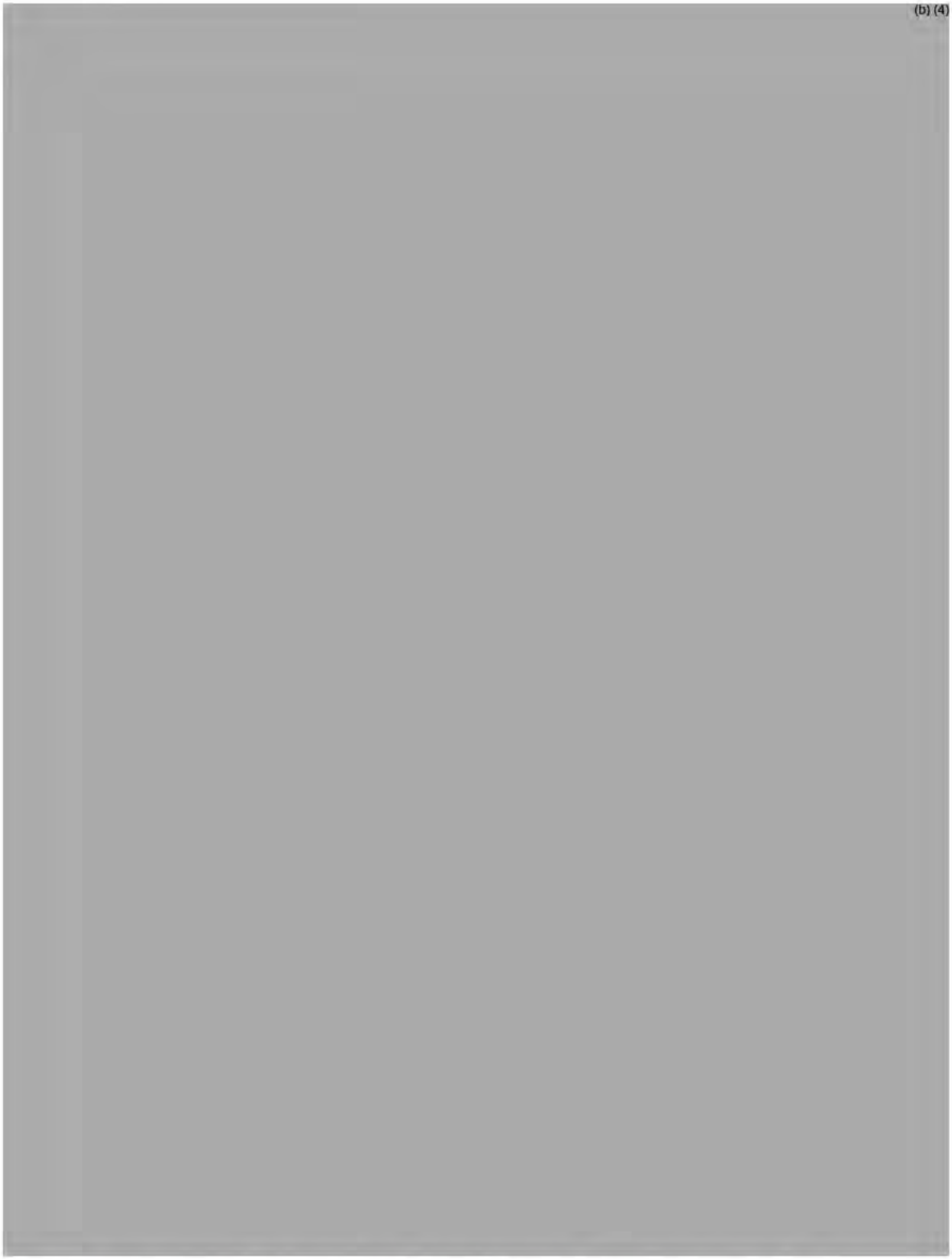
Facility -9



OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA202153

Michael Klapal
4/18/16

Secondary Review Comments and Concurrence:

I concur with Mr. Klapal's recommendations.

Vidya Pai
4/26/2016

Tertiary Review Comments and Concurrence:

I concur with the above recommendations.
Krishna Ghosh
5/16/2016

MEMORANDUM to FILE

To: NDA **202–153**

From: David A. Place, PhD Reviewing Chemist

Through: Eldon Leutzinger, PhD, Chemistry Lead

Through: Eric Duffy, PhD Director, ONDQA Division III

Subject: CMC Comparison of Labeling (Package Insert) and User Manual Documents for RubyFill

Date: December 29, 2014

Background – Jubilant DraxImage has submitted two key Amendments to NDA 202–153 that relate to the preparation and use of the Drug Product – both an updated Package Insert as well as a User Manual.

The titles, filenames, DARRTS submissions, and filing dates of these documents are as follows:

- Package Insert 1 14 1 3 Package Insert (clean) (2).doc SDN # 16 9/23/2013
- User Manual user–manual 18MAR2014.pdf SDN # 19 3/25/2014

The Table of Contents of both documents are reproduced on the following pages.

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

/s/

DAVID A PLACE
12/11/2014

ELDON E LEUTZINGER
12/11/2014

RAMESH RAGHAVACHARI
12/11/2014
for Eric Duffy

MEMORANDUM to FILE

To: NDA **202–153**

From: David A. Place, PhD Reviewing Chemist

Through: Eldon Leutzinger, PhD, Chemistry Lead

Through: Eric Duffy, PhD Director, ONDQA Division III

Subject: Review Update

Date: December 10, 2014

Background – The following document contains several updates based on the 9/17/2014 Primary CMC review.

Note that the review cover page lists identifies the submission as an **ANDA**. After receipt, the submission was reclassified as an **NDA**. The review was done for the Division of Medical Imaging, not the Office of Generic Drugs.

H. Post–Approval Stability Protocol and Commitment – Post-approval, the sponsor proposes to carry out (b) (4) the proposed protocol below.

(b) (4)

The deletion of this sentence will improve consistency with the actions CMC will recommend to the sponsor.

Deficiencies to Communicate – ***(Suggested additions are in bold italic type).***

The post–approval testing protocol needs to be more rigorous. (b) (4) [redacted]

(b) (4) [redacted]

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

/s/

DAVID A PLACE
12/11/2014

ELDON E LEUTZINGER
12/11/2014

RAMESH RAGHAVACHARI
12/11/2014
for Eric Duffy

Review of Chemistry, Manufacturing, and Controls

NDA 202–153

Ruby–Fill®

Jubilant DraxImage, Inc.

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Quality Assessment III Branch IX

for

Clinical Review Division: HFD–160

Division of Medical Imaging
and
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA 202–153

2. REVIEW # 1

3. REVIEW DATE: 17–SEP–2014

4. REVIEWER: David A. Place, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	18–JUN–2010
Amendment	19–MAY–2011
Labeling Amendment (Container)	20–DEC–2011
Labeling Amendment (Package Insert)	25–OCT–2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	PO Box 1000, Montville, NJ 07045–1000
Representative:	Philip Johnson, Deputy Director, Global Regulatory Affairs
Telephone:	(973) 487–2181

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby–Fill®
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: NA
- Submission Priority: NA

9. LEGAL BASIS FOR SUBMISSION: Not Applicable to NDAs

10. PHARMACOLOLGICAL CATEGORY/INDICATION: Cardiac Positron Emission Tomography

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY:

13. ROUTE OF ADMINISTRATION: IV

14. Rx /OTC DISPENSED: _X_ Rx ____ OTC

Reference ID: 3624490
539 of 1085

15a. SPOTS (Special Products On–Line Tracking System)

_____SPOTS product – Form Completed __X__ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCTS: Not Applicable

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: $^{82}RbCl$
Molecular Weight: 117.5 daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: NA

DMF #	Type	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	3	Adequate	1/18/2012	Updated 4/17/2012
	II			3	Adequate	1/18/2012	Updated 8/31/2012

a Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

Patent: NA

Exclusivity: NA.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/16/2014	OC
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	Acceptable per this CMC review	9/17/2014	D. Place
DMEPA	Acceptable	4/2/2014	M. Rutledge
EA	Categorical Exclusion – Acceptable	9/17/2014	D. Place
Microbiology	Acceptable	2/29/2012	D. Palmer–Ochieng
DMIP/safety	Deficiencies Identified	6/27/2014	I. Krefting

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): ***Not Applicable***

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 202–153

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202–153 is not recommended for approval from a CMC standpoint until a complete response on identified CMC deficiencies is received from the sponsor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The Ruby-Fill® 82Sr/82Rb generator provides an eluted solution of the drug substance, Rubidium Rb82 Chloride Injection in sterile normal saline. ^{82}Rb is produced on the generator by the radioactive decay of ^{82}Sr. ^{82}Sr remains bound to the column while ^{82}Rb is eluted from the column as RbCl with 0.9% sodium chloride.

^{82}Rb decays by positron emission with a half-life of 1.273 minutes (76.38 sec) to stable ^{82}Kr gas. Due to this very short half–life, the Ruby–Fill elution system will be located in very close proximity to directly dose the patient being imaged to allow prompt injection of the Rubidium–82 eluate. Also, due the short half–life (as with other PET radioisotopes), proactive sterility controls must be in place.

B. Description of How the Drug Product is Intended to be Used

It is indicated as an agent for positron emission tomography (PET) imaging, specifically for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease, as the Rubidium ions mimic the cardiac biological function of Potassium ions. As this product involves a radionuclide generator and a product delivery device (b) (4) there are two important issues: (1) how the (b) (4) works with the generator and (2) the nature of the various factors underlying user interaction with the system to assure operation of the system to produce a safe product. Accordingly, consults are requested for CDRH Device Engineering and CDRH Human Factors Assessment.

C. Basis for Approvability or Not-Approval Recommendation

A critical CMC issue has been identified in the Chemistry sections of the submission. The level of post–approval testing proposed is inadequate. (b) (4)

III. Administrative

A. Reviewer's Signature

Chemist	David A. Place, PhD	_____	Date: 17-SEP-2014

B. Endorsement Block

Chemistry Lead	Eldon Leutzinger, PhD	_____	Date:
Division Director	Eric P. Duffy, PhD	_____	Date:

cc: Orig. NDA 202–153
HFD–160

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	ANDA202153/000	**Sponsor:**	DRAXIMAGE
Org. Code:	600		7361 CALHOUN PL STE 500
Priority:			ROCKVILLE, MD 20855
Stamp Date:	30-JUN-2010	**Brand Name:**	
PDUFA Date:	30-APR-2011	**Estab. Name:**	RUBIDIUM CHLORIDE RB 82
Action Goal:		**Generic Name:**	
District Goal:	01-MAR-2011	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; GENERATOR; RUBIDIUM CHLORIDE RB-82; (b) (4) mCi	

FDA Contacts:	R. D COSTA	Prod Qual Reviewer	(HFD-623)	2402768407
	M. GONITZKE	Product Quality PM	(HFD-600)	2402768422
	D. DOAN	Regulatory Project Mgr	(HFD-617)	2402769336
	ID = 109049	Team Leader		

Overall Recommendation:	ACCEPTABLE	on 16-JAN-2014	by T. WILSON	()	2404024226
	PENDING	on 02-OCT-2013	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	3009003838
	JUBILANT DRAXIMAGE INC 16751 RTE TRANS CANADA KIRKLAND, , CANADA H9h 4j4		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	POSITRON EMISSION TOMOGRAPHY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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(b) (4)

[redacted]

Batch Records – Executed, bilingual batch records have been submitted, fully reflecting the manufacturing process and controls.

Satisfactory.

Labeling – The PACKAGE INSERT contains the following black box warning:

(b) (4)

[redacted]

Satisfactory. The Package Insert is equivalent to the reference listed drug.

Container Labels – Since Ruby–Fill is radioactive, there are no internal labels.

Outer Main Label – This label is applied to the lead "pig". It is general in nature.

Satisfactory. Note: None of the labeling (b) (4)

(b) (4)

Deficiencies to Communicate –

The post–approval testing protocol needs to be more rigorous. (b) (4)

(b) (4)

Reference ID: 3624490
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/s/

DAVID A PLACE
09/17/2014

ELDON E LEUTZINGER
09/17/2014

ERIC P DUFFY
09/19/2014

Initial Quality Assessment (IQA)
For
Division of New Drug Quality Assessment III, Branch VII
Office of New Drug Quality Assessment

OND Division: OGD
ANDA: 202-153
Applicant: Draximage
16751 Autoroute Transcanadienne / Trans-Canada Highway
Kirkland(Quebec) Canada H9H 4J4
Stamp Date: 06/30/2010
Trademark: Ruby-Fill
USAN: None
INN: None
Company Code: None
Established: Rubidium Rb 82 Generator
Dosage Form: Sterile solution
Route of Administration: IV
Indication: assessment of regional myocardial perfusion [redacted] (b) (4)

CMC Lead: Eldon E. Leutzinger, Ph.D., Branch VII

ONDQA Fileability (N/A) YES NO
(OGD function)

Comments for 74-Day Letter: N/A

Summary and Critical Issues:

A. Summary

The **Drug Product** (Ruby-Fill) is a radionuclide generator (Rubidium Chloride Rb 82 Generator) that contains at calibration [redacted] (b) (4) $^{82}SrCl_2$ adsorbed onto hydrous [redacted] (b) (4) stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces Rubidium Chloride Rb 82 Injection USP. It contains [redacted] (b) (4) $^{82}RbCl$ activity delivered depends on the elution rate and the amount of volume eluted, based on the intended dose, as well as (of course) the amount of $^{82}SrCl_2$ adsorbed onto the column. [redacted] (b) (4)
the set up is shown as follows. See the next review page.

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Reference ID: 3222430
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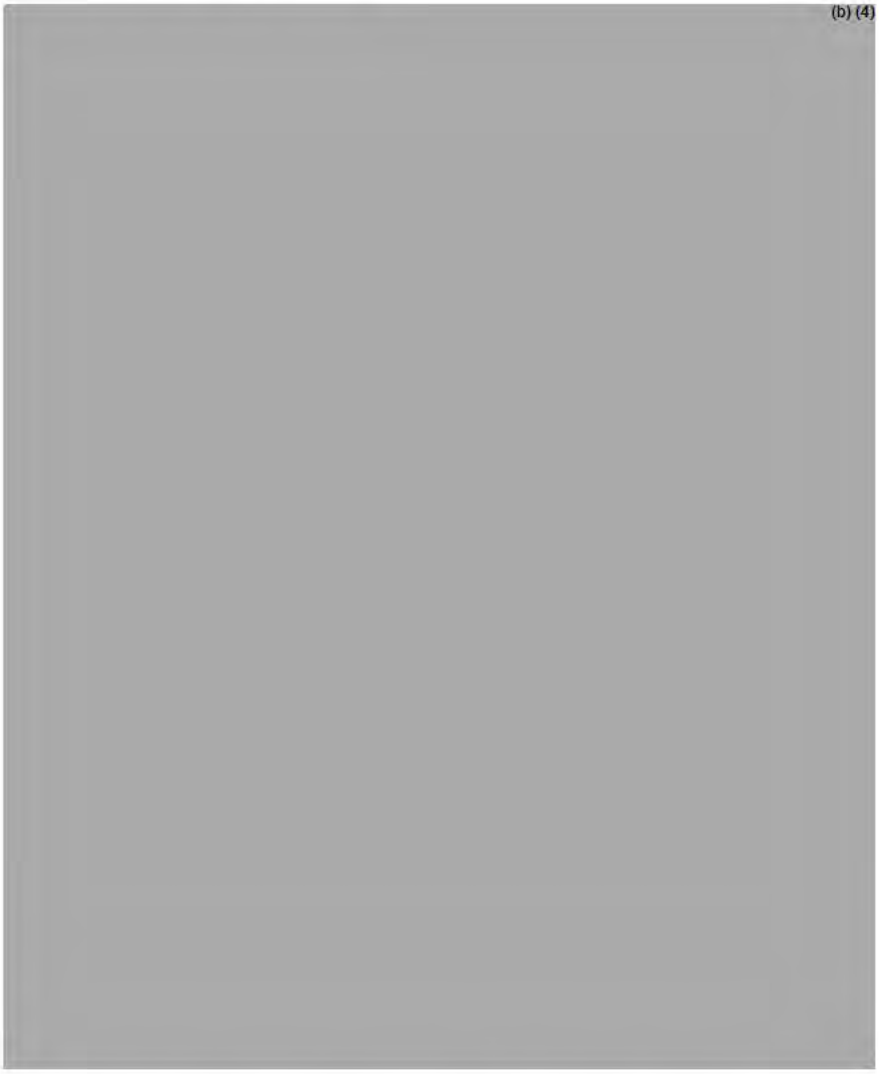
In this IQA, I have not tried to capture all of the considerations and issues that might be involved in this ANDA, but have tried to identify those issues I think are most important and in particular in relation to ^{82}Sr breakthrough, since it relates most severely to generator column performance.

Manufacturing Facilities:



CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 11/27/2012
Division of New Drug Quality Assessment III, Branch VII

Division Director: Eric Duffy, Ph.D.
Division of New Drug Quality Assessment III

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/s/

ELDON E LEUTZINGER
11/28/2012

ERIC P DUFFY
12/12/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

September 15, 2016

NDA: 202153

Drug Product Name
Proprietary: Ruby-Fill® (Rubidium Rb-82 Generator)
Non-proprietary: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/28/2015	12/30/2015	N/A	1/7/2016
6/11/2016	6/15/2016	N/A	6/15/2016
8/16/2016	8/17/2015	N/A	8/17/2016

Applicant/Sponsor
Name: Jubilant DraxImage Inc.
Address: 16751 Trans-Canada Highway
Kirkland, Quebec
Canada H9H4J4
Representative: Susan P. Spooner, Ph.D.
Telephone: 919-745-2492
Fax: 513-763-7628

Name of Reviewer: Yeissa Chabrier-Roselló, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION** NDA Resubmission

2. **SUBMISSION PROVIDES FOR:** Response to CMC deficiencies in Agency's Complete Response letter

3. **MANUFACTURING SITE:**
Jubilant DraxImage Inc.
16751 TransCanada Highway
Kirkland, QC
Canada H9H4J4

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Generator for PET parenteral solution ((b) (4) mCi), delivered intravenously

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

B. **SUPPORTING/RELATED DOCUMENTS:**
N202153typeCmeetingR1.pdf review by J. Cole dated 7/22/2015
202153.doc by D. Palmer dated 1/3/2011
202153a1.doc by D. Palmer dated 2/29/2012

C. **REMARKS:** This is an eCTD submission. This review covers the responses for the complete response letter sent on 12/18/2014. The meeting package memo N202153typeCmeetingR1.pdf (dated 7/22/2015) by J. Cole is referenced in this review. The review also references the teleconference with the firm on 5/5/2016 pertaining to the dye ingress testing to assess patient cross-contamination during the drug product's shelf-life of 60 days. Subsequently, an information request was sent regarding these issues on 5/26/2016, and is referenced in this review; the information request response was received 6/15/2016. A subsequent information request was sent in July 2016 which was followed by a teleconference with the sponsor on 7/13/2016. This review includes the two information requests and corresponding information request responses (6/17/2016 & 8/17/2016). The review of the two information request responses is located at the end of this review.

Filename: 202153-FINAL.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a rubidium generator for intravenous delivery of the PET parenteral solution ((b) (4) mCi). The drug product/generator is to be used continuously for up to 60 days. (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☒ Yes ☐ No

III. Administrative

A. Reviewer's Signature _____

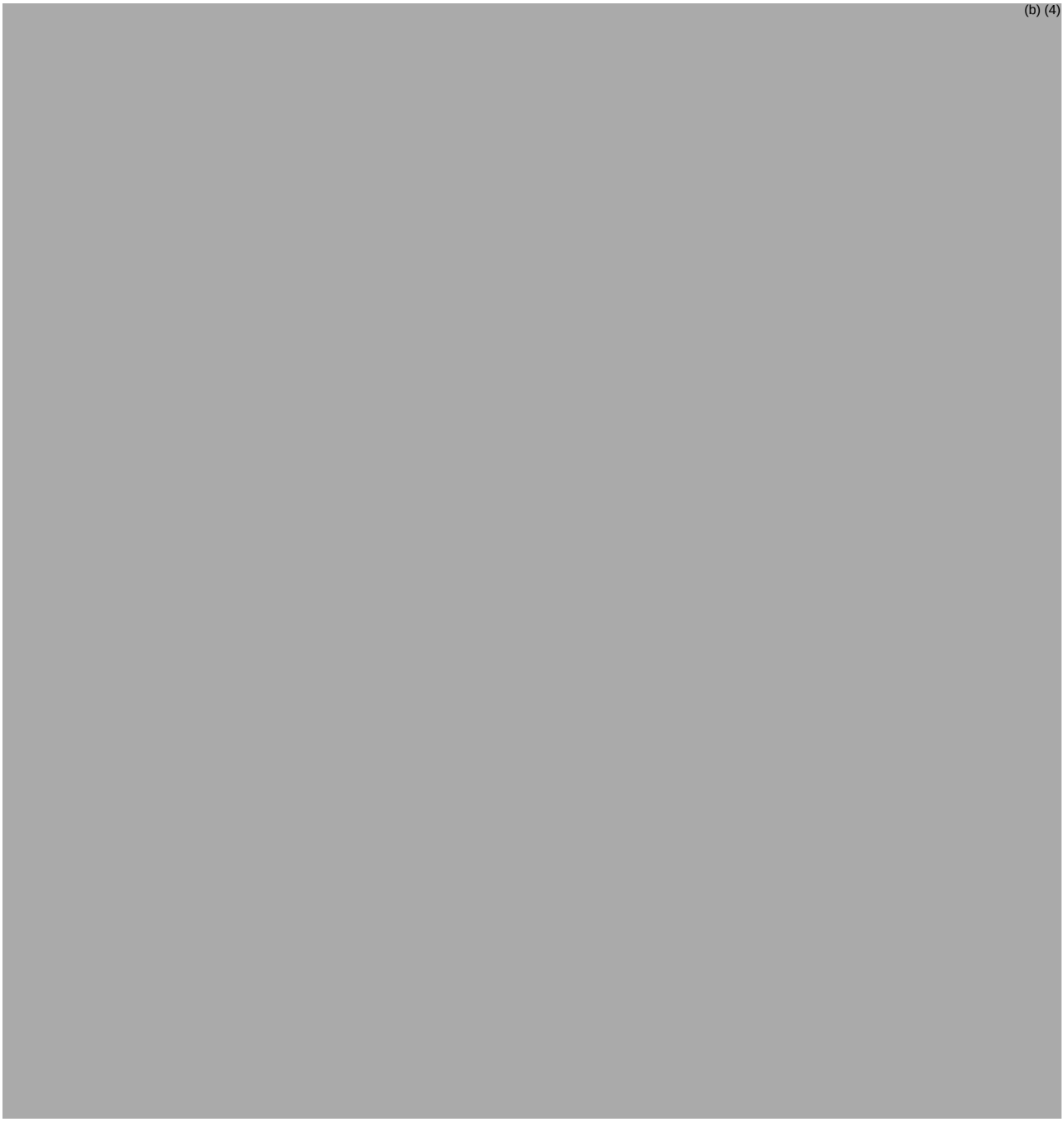
B. Endorsement Block
Microbiologist/Yeissa Chabrier-Roselló, Ph.D.
Microbiology Secondary Reviewer/Jessica Cole, Ph.D.

C. CC Block
cc: Field Copy /Panorama

Product Quality Microbiology Assessment

The subject NDA resubmission (submitted December 30, 2015) provides responses to the product quality and the infection control for the subject drug product. For the purpose of this review, only the deficiencies and/or relevant deficiency parts that pertain to the microbiology assessment/sterility assurance of the subject drug product are reviewed below. The deficiencies, which are italicized below, were drafted by the original CDRH reviewer and conveyed to the firm in the Agency's 12/18/2014 complete response letter. Additionally, the information requests sent on 5/26/2016 and July 2016 and the corresponding responses are reviewed at the end of this document.

(b) (4)



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APPEARS THIS WAY ON ORIGINAL

Product Quality Microbiology Review

June 3, 2016

NDA: 202153

Drug Product Name
Proprietary: Ruby-Fill® (Rubidium Rb-82 Generator)
Non-proprietary: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/28/2015	12/30/2015	N/A	1/7/2016

Applicant/Sponsor
Name: Jubilant DraxImage Inc.
Address: 16751 Trans-Canada Highway
Kirkland, Quebec
Canada H9H4J4
Representative: Susan P. Spooner, Ph.D.
Telephone: 919-745-2492
Fax: 513-763-7628

Name of Reviewer: Yeissa Chabrier-Roselló, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION** NDA Resubmission

2. **SUBMISSION PROVIDES FOR:** Response to CMC deficiencies in Agency's Complete Response letter

3. **MANUFACTURING SITE:**
Jubilant DraxImage Inc.
16751 TransCanada Highway
Kirkland, QC
Canada H9H4J4

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Generator for PET parenteral solution ((b) (4) mCi), delivered intravenously

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

B. **SUPPORTING/RELATED DOCUMENTS:**
N202153typeCmeetingR1.pdf review by J. Cole dated 7/22/2015
202153.doc by D. Palmer dated 1/3/2011
202153a1.doc by D. Palmer dated 2/29/2012

C. **REMARKS:** This is an eCTD submission. This review covers the responses for the complete response letter sent on 12/18/2014. The meeting package memo N202153typeCmeetingR1.pdf (dated 7/22/2015) by J. Cole is referenced in this review. The review also references the teleconference with the firm on 5/5/2016 pertaining to the dye ingress testing to assess patient cross-contamination during the drug product's shelf-life of 60 days. Subsequently, an information request was sent regarding these issues on 5/26/2016, and is referenced in this review.

Filename: 202153.doc

Reference ID: 4001415
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Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a rubidium generator for intravenous delivery of the PET parenteral solution ((b) (4) mCi). The drug product/generator is to be used continuously for up to 60 days. (b) (4)

B. Brief Description of Microbiology Deficiencies –
Please see letter of deficiency in Section 3 of this review.

C. Assessment of Risk Due to Microbiology Deficiencies – High

D. Contains Potential Precedent Decision(s) - ☒ **Yes** ☐ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Yeissa Chabrier-Roselló, Ph.D.
Microbiology Secondary Reviewer/Jessica Cole, Ph.D.

C. CC Block
cc: Field Copy /Panorama

Reference ID: 4001415
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Product Quality Microbiology Assessment

The subject NDA resubmission (submitted December 30, 2015) provides responses to the product quality and the infection control for the subject drug product. For the purpose of this review, only the deficiencies and/or relevant deficiency parts that pertain to the microbiology assessment/sterility assurance of the subject drug product are reviewed below. The deficiencies, which are italicized below, were drafted by the original CDRH reviewer and conveyed to the firm in the Agency's 12/18/2014 complete response letter.

(b) (4)

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3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

NDA: 202153 APPLICANT: Jubilant DraxImage Inc.

DRUG PRODUCT: Ruby-Fill® (Rubidium Rb-82 Generator)

Microbiology Deficiencies:

The studies and results provided for the dye ingress test of the Ruby-Fill system's components, as currently designed, (b) (4) demonstrates that the patient cross-contamination risk has not been fully mitigated by the system's current safety features. We acknowledge the Hazard analysis and justification in the submission for why these results do not pose a risk to patients; however, we disagree with the conclusions and assessments. The studies provided did not perform in a predictable way. (b) (4) A scientific explanation regarding the referenced studies and results was not provided in the validation report or during the teleconference on 5/5/2016. As discussed in said teleconference, the Agency has serious concerns with the dye ingress system/methodology used. The results, data analysis and interpretations for the dye ingress test results provided in document "Appendix 9-3 Dye Ingress Testing Report.pdf" are of concern to the Agency. Therefore, we request that the following points be addressed in subsequent studies to better assess the risk of patient cross-contamination with the current design for the Ruby Fill system. The studies should show (b) (4)

i. Provide dye ingress test studies (b) (4) .

ii. Clearly state the in-use parameters proposed for patient administration to include (b) (4) conditions. If the conditions used for the dye ingress test are different (e.g. worst case) to the in-use parameters, provide a rationale.

iii. Include a description of the negative and positive controls for the studies. It is expected that the test will demonstrate 100% efficacy (b) (4)

Reference ID: 4001415
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[redacted] (b) (4)

iv. Provide the limit of detection for the dye ingress assay.

v. Describe the function and design of the [redacted] (b) (4) system component, which reduce the risk of patient cross-contamination. Give operational characteristics [redacted] (b) (4) and any other relevant characteristics [redacted] (b) (4) Indicate the location for each of these components during the proposed in-use time with a diagram.

vi. Describe the limitations of the dye ingress test in terms of fluid properties that may influence dye transport compared to viral and bacterial transport.

Yeissa Chabrier Rosello -S

Digitally signed by Yeissa Chabrier Rosello -S
Date: 2016.06.03 14:28:19 -04'00'

Jessica Cole -S

Digitally signed by Jessica Cole -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica Cole -S, 0.9.2342.19200300.100.1.1=2000397920
Date: 2016.06.03 14:31:20 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 21 July 2015

TO: Frank Lutterodt
Regulatory Business Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(301) 796-5148

THROUGH: Stephen Langille, PhD
Microbiology Branch Chief
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: NDA: 202-153
Submission Date: 17 June 2015 (received 19 June 2015)
Drug Product: Ruby-Fill (Rubidium Rb 82 Generator)
Applicant: Jubilant Draximage, Inc.

A product quality microbiology review of the meeting package for NDA 202-153 is complete. This meeting package is a follow up to the Type A meeting package received on 18 February 2015 and the associated microbiology review dated 17 April 2015. The Type A meeting request was submitted after issuance of the 18 December 2014 complete response letter.

The applicant has submitted a summary of studies to address microbial contamination and patient-to-patient cross contamination issues raised in the complete response letter. Appendices 14-16 contain the proposed testing strategies.

Appendix 13- 3000061-D v01 Device Description
This document describes the design of the elution system. (b) (4)

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/s/

JESSICA COLE
07/22/2015

STEPHEN E LANGILLE
07/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 31 March 2015

TO: Frank Lutterodt
Regulatory Health Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(301) 796-5148

THROUGH: Stephen E. Langille, PhD
Acting Branch Chief
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: NDA: 202-153
Submission Date: 13 February 2015
Drug Product: RUBY-FILL (Rubidium Rb-82 Generator)
Applicant: Jubilant Draximage Inc.

A product quality microbiology review of the Type A meeting package for NDA 202-153 is complete. This NDA described a PET drug product (generator) intended for intravenous administration. This NDA was originally submitted as ANDA 202-153 and was recommended for approval on the basis of sterility assurance by a microbiology reviewer from the Office of Generic Drugs. That review found the sterility assurance information acceptable (b) (4) The microbiology review did not assess the risk for use according to the proposed product insert (b) (4)

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/s/

JESSICA COLE
04/16/2015

STEPHEN E LANGILLE
04/17/2015

Product Quality Microbiology Review

December 15, 2014

NDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Rb 82 Chloride for Injection

Review Number: #3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/23/13	9/24/13	N/A	4/11/14

Submission History (for ANDA amendments only): N/A

Submit Date	Microbiology Review #	Review Date(s)
6/18/10	1	11/1/2010
5/18/11	2	5/27/11
8/29/11		

Applicant/Sponsor
Name: Jubilant Draximage Inc.
Address: 16751 TransCanada Highway, Kirkland, Quebec, Canada H9H 4J4

U.S. Agent
Name: Greg Hockel and Dr. Norma LaFrance
Address: 7361 Calhoun Place Suite 500, Rockville, MD 20855-2765
Telephone: (301) 926-6148/(514) 235-8754; Fax: (30) 838-3182/(514) 694-9295

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Gratuitous Amendment.

2. SUBMISSION PROVIDES FOR: Gratuitous labeling information with sterility assurance relevance

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission. The applicant's 9/23/13 gratuitous amendment was consulted to be reviewed by Dat Doan from OGD/DLPS because a BlackBox warning was added to the package insert. No other labeling changes from that provided in the initial submission are indicated in the 9/23/13 amendment. The original submission was an ANDA that was converted to a NDA on 4/9/13. The original microbiology review (202153a1.doc dated 5/27/11 by D. Palmer) was recommended for approval based on sterility assurance of the drug product. The US agent(s) shown above on page 1 of this review was obtained from the most recent 5/12/14 submission that does not contain microbiology information.

Filename: 202153a2.doc
Template version: OGD modified_AP_2013v3.doc

Reference ID: 3673024
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Executive Summary

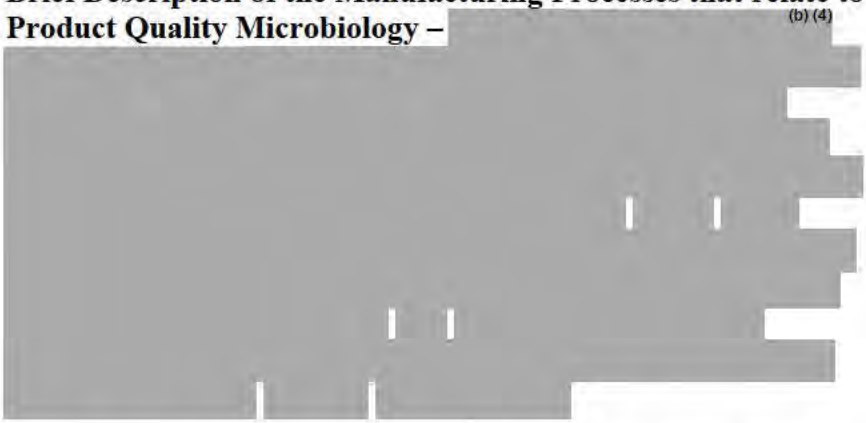
I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)



B. Brief Description of Microbiology Deficiencies –None identified.

C. Assessment of Risk Due to Microbiology Deficiencies – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Marla Stevens-Riley, Ph.D.
Microbiology Division Director (Acting)/Lynne Ensor, Ph.D.

C. CC Block
cc: Field Copy

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Product Quality Microbiology Assessment

The applicant's 9/23/13 gratuitous amendment was consulted to be reviewed by Dat Doan from OGD/DLPS because a BlackBox warning was added to the package insert. No other labeling changes from that provided in the initial submission are indicated in the 9/23/13 amendment. The original submission was an ANDA that was converted to a NDA on 4/9/13. The original microbiology review (202153a1.doc dated 5/27/11 by D. Palmer) was recommended for approval based on sterility assurance of the drug product.

The drug product (Rubidium Rb 82 chloride injection) consists of a (b) (4) Ruby-Fill™ generator column that produces Rb-82 by the decay of Strontium-82 (Sr-82), and an accessory elution system (b) (4) A black box label has been added to the package insert in the October 25, 2012 submission; however, the September 23, 2013 submission contains a reformatted version of the labeling. The BlackBox warning in the updated package insert contains user information to prevent unintended radiation exposure during elution and delivery of the eluate to the patient, and specifies that the generator must be discarded when the following conditions (named "expiration limits" by the applicant) are exceeded: 30 L of cumulative generator eluate volume, 60 days post generator calibrator date, Sr-82 and Sr-85 levels of 0.01μCi/mCI Rb-82 and 0.1μCi/mCI Rb-82 respectively in the generator eluate.

Note to Reviewer: User information in the labeling Blackbox warning including expiration limits for the generator, are provided to prevent unintended radiation exposure during elution from the generator and delivery of the drug product to the patient, and should not adversely affect the sterility assurance of the drug product.

Acceptable

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

/s/

DUPEH G Palmer-Ochieng
12/15/2014

EILEEN T MONAGHAN
12/17/2014

MARLA K STEVENS RILEY
12/17/2014

LYNNE A ENSOR
12/17/2014

Product Quality Microbiology Review

May 27, 2011

ANDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Chloride Rb 82 Generator

Review Number: #2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
5/18/2011	5/19/2011	N/A	5/23/2011
8/29/11	9/1/11	N/A	9/2/11

Submission History (for amendments only): N/A

Submit Date	Microbiology Review #	Review Date(s)
06/18/2010	1	11/1/2010

Applicant/Sponsor
Name: Draximage
Address: 16751 Trans Canada Highway,
Kirkland, Quebec, Canada H9H 4J4

U.S. Agent: Kendle International Inc.
7361 Calhoun Place Suite 500
Rockville, MD 20855-2765

Representative: Hari Nagaradona, Director Regulatory Affairs
Telephone: (301) 296 1370

Name of Reviewer: Dupeh Palmer Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.