AtomVie
Global Radiopharma

Radiotherapeutics CDMO (Spin-off of cpdc Centre for Probe Development and Commercialization)

Medical Isotope Regulatory Considerations

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2023 TRTR & IGORR Conference, University of Maryland

June 22, 2023

AtomVie Global Radiopharma Inc. - Background

Radiopharmaceutical (RP) Contract Development Manufacturing Organization (CDMO)

- Located in Hamilton, Ontario, Canada
- Formed in 2022 (for profit spinoff of Centre for Probe Development and Commercialization)
- >30 RP development & supply projects since 2011
  - Experienced with **Ac-225, I-131, In-111, Lu-177, Zr-89** RP production (but can work with effectively any isotope)
  - Large (top 20) and small RP clients
  - Leadership team: collectively 50+ years in radiopharma
- Currently supply >10 products to trials in 17 countries
- Also **manufactures n.c.a. Lu-177** (Isotopia Molecular Imaging, Israel) and interested in partnering with other medical isotope suppliers
- Helped set up Quality Management Systems for 4 clients

Photo of new >60,000 sq ft facility under construction for global investigational & commercial therapeutic RP supply (expected 2025-2026)

AtomVie Regulatory Affairs

AtomVie's Regulatory Affairs Department has collectively **20 years' experience** successfully registering investigational and commercial radiopharmaceuticals

Experience with both small and big pharma clients, and institutions

Expertise in both:
- **Diagnostic products** (e.g., F-18, Ga-68)
- **Therapeutic products** (e.g., Lu-177, Ac-225)

Successful commercial registrations:
[F-18]-FDG (ANDA - FDA) and
[Ga-68]-DOTATATE (NDS - Health Canada)

>99%

>99.5% success rate filing over 375 submissions to **Health Canada and the FDA** (all filings submitted and approved/cleared on target)

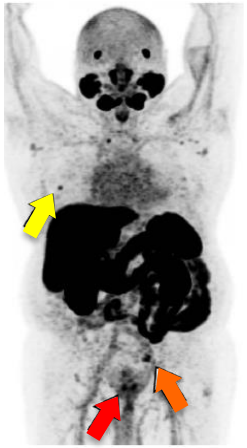
Medical Isotope experience: drafted or reviewed **Ge-68 generator and Lu-177 registrations**

Extensive **Drug Master File experience with FDA (1) and Health Canada (8)**

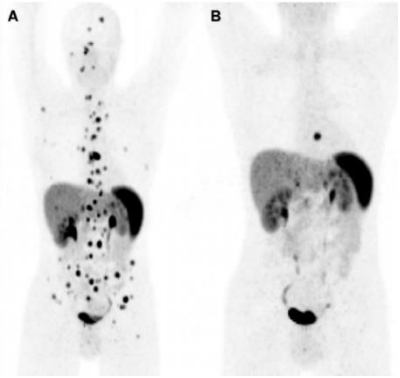
>150 quality-related submissions filed with FDA or Health Canada

Medical Isotope Background

- **Commonly used medical isotopes**
  - **[Diagnostic; PET or SPECT]** F-18, Ga-68, In-111, Tc-99m
  - **[Therapeutic]** Ac-225, I-131, Lu-177, Ra-223
- **Terminology**
  - ***CMC:*** chemistry, manufacturing and controls (quality information)
  - ***Critical raw material (CRM):*** medical isotope and ligand = extensive CMC information needed
  - ***Drug substance (DS):*** the active pharmaceutical ingredient (API) that elicits the intended pharmacological or diagnostic effect
  - ***Drug product (DP):*** the presentation of the product (DS + excipients in final dosage form)
- Some medical isotopes (e.g., Tc-99m) can also be directly used as a DP



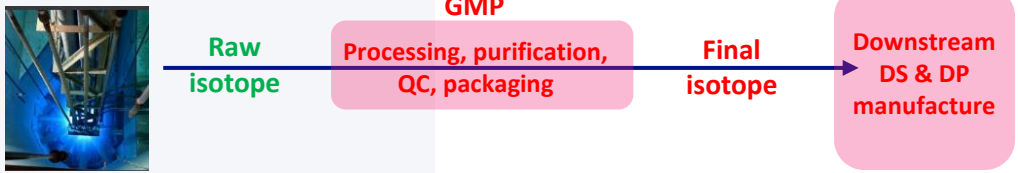
18F-PSMA-1007 PET showing prostate cancer local relapse in prostate (red), and bone metastases in lower spine (orange) & rib (yellow); Witkowska-Paneta 2019, *Clin Nucl Med,* 44(12)



^{68}Ga-DOTATOC PET images pre- and post-tx with ^{177}Lu-DOTATATE & ^{90}Y-DOTATOC (atypical carcinoid). Prasad 2015, *EJNMMI Research* 5(1)

Underlying Quality Requirements

- Isotopes used in human DPs should follow **current Good Manufacturing Practices (cGMP)**
  - Underlying **Quality Management System (QMS)**
  - Should have independent Quality Assurance role(s)
  - Same requirements apply for DS's & DP's
  - Generally, creation of the raw isotope is not considered GMP, but subsequent processing/testing is (if applicable)



GMP definitions/resources
- [US] 21 CFR 210, 211
- [CAN] Food & Drug Regs, Part C, Division 2
- Regulator guidance documents
- International Conference on Harmonization (ICH) Q7

Regulatory Submissions: Crash Course

- **Common Technical Document (CTD)**
  - Global format (**Modules 2-5; "m2-5"**) defined by ICH M4
  - **Module 1 ("m1")**: specific to jurisdiction
- Since 2017, **electronic (eCTD) format** required:
  - **Documents:** ToC, headings, bookmarks, intra-doc links
  - **Submission:** electronic backbone, viewing software, meta-data, inter-doc links
- Regulatory lifecycle (drug products)
  - **Investigational New Drug (IND): Phase 1** (safety-focused) → **Phase 2** (proof-of-concept) → **Phase 3** (pivotal trial(s))
  - **New Drug Application (NDA; commercial):** show the product is of high quality, safe and effective
  - **Maintenance:** assess/register changes to product, pharmacovigilance

NDS (CAN) for [F-18]-FDG

CMC Information

- Regulators typically medical isotopes like a DS/API and expect a similar level of CMC info
  - **[Phase 1-2]** A Certificate of Analysis (CoA) documenting the testing performed + a statement it's manufactured following GMP may suffice
  - **[Phase 2-3 & commercial]** Full CMC information should be submitted to the regulator
- Goal: show product can be consistently produced meeting acceptable specifications (notably identity and purity)
- Level of detail typically increases from Phase 1 → Phase 2 → Phase 3/commercial
- Placed in **Module 3.2.S ± 2.3** (Quality Overall Summary or "QOS")

[32S1] General Info: Name, Structure, Physicochemical Properties

[32S2] Manufacture: Manufacturer, Mnfing Process, Control of Materials and Critical Steps/ Intermediates, Process Validation & Development

[32S3] Characterization: Elucidation of Structure and Other Characteristics, Impurities

[32S4] Control of DS: Specifications, Analytical Methods, Validation of Methods, Batch Analyses, Justification of Specifications

[32S5] Reference Standards

[32S6] Container Closure System

[32S7] Stability: Summary & Conclusions, Data

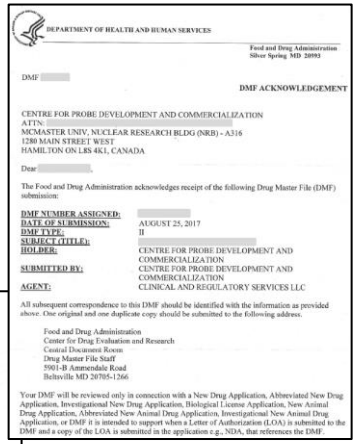
[32A] Facilities and Equipment
[32R] Supporting Info

Registering CMC Information

Drug Master File (DMF)

- DMF Owner submits CMC info directly to regulator
- Applicant (customer) references DMF (via a **Letter of Access (LoA)**), without direct access, for their IND/NDA/BLA
- DMF must be amended, and applicants notified to file appropriate update, when any changes made
  - **[US]** Annual Report must be filed each year
- Technical review of DMF by FDA occurs
  - **[Parent DMF]** When 1st applicant files linked submission
  - **[Amended DMF]** When all applicants file linked updates
  - If any questions, FDA will contact DMF Owner directly
  - DMF Owner must wait until all applicants receive approval for parent/major changes, and (ideally) wait until they've submitted minor changes
- DMF process very similar in Canada

FDA DMF Acknowledgement Letter →



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

DMF

DMF ACKNOWLEDGEMENT

CENTRE FOR PROBE DEVELOPMENT AND COMMERCIALIZATION
ATTN:
MCMASTER UNIV, NUCLEAR RESEARCH BLDG (NRB) - A316
1280 MAIN STREET WEST
HAMILTON ON L8S 4K1, CANADA

Dear

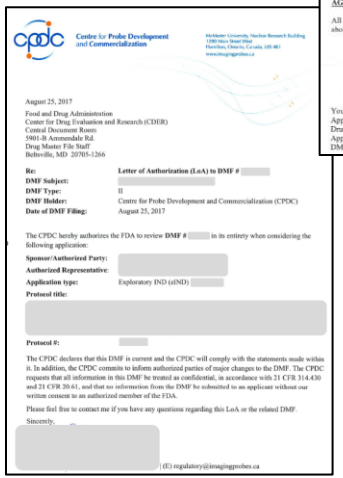
The Food and Drug Administration acknowledges receipt of the following Drug Master File (DMF) submission:

DMF NUMBER ASSIGNED:
DATE OF SUBMISSION: AUGUST 25, 2017
DMF TYPE: II
SUBJECT (TITLE):
HOLDER: CENTRE FOR PROBE DEVELOPMENT AND COMMERCIALIZATION
SUBMITTED BY: CENTRE FOR PROBE DEVELOPMENT AND COMMERCIALIZATION
AGENT: CLINICAL AND REGULATORY SERVICES LLC

All subsequent correspondence to this DMF should be identified with the information as provided above. One original and one duplicate copy should be submitted to the following address.

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville MD 20705-1266

Your DMF will be reviewed only in connection with a New Drug Application, Abbreviated New Drug Application, Investigational New Drug Application, Biological License Application, New Animal Drug Application, Abbreviated New Animal Drug Application, Investigational New Animal Drug Application, or DMF it is intended to support when a Letter of Authorization (LOA) is submitted to the DMF and a copy of the LOA is submitted in the application e.g., NDA, that references the DMF.



cpdc Centre for Probe Development and Commercialization

August 25, 2017

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Central Document Room
5901-B Ammendale Rd.
Drug Master File Staff
Beltsville, MD 20705-1266

Re: **Letter of Authorization (LoA) to DMF #**
DMF Subject:
DMF Type: II
DMF Holder: Centre for Probe Development and Commercialization (CPDC)
Date of DMF Filing: August 25, 2017

The CPDC hereby authorizes the FDA to review **DMF #** in its entirety when considering the following application:

Sponsor/Authorized Party:
Authorized Representative:
Application type: Exploratory IND (eIND)
Protocol title:

Protocol #:

The CPDC declares that this DMF is current and the CPDC will comply with the statements made within it. In addition, the CPDC commits to inform authorized parties of major changes to the DMF. The CPDC requests that all information in this DMF be treated as confidential, in accordance with 21 CFR 314.430 and 21 CFR 20.61, and that no information from the DMF be submitted to an applicant without our written consent to an authorized member of the FDA.

Please feel free to contact me if you have any questions regarding this LoA or the related DMF.

Sincerely,

(E) regulatory@imagingprobes.ca

← Letter of Access (LoA)

What Does This All Mean?

- **Quality Management System**
  - Budget **~7-9 months** to set up and **~3 months** to train on & activate the system; could do this in a staggered fashion
  - Consultants can help set up and audit ± manage your QMS; also consider in-house Quality Assurance (QA) staff
  - FDA unlikely to audit at IND stage, but they will probably audit if you have a customer at NDA/BLA stage; similar situation in Canada
- **Drug Master File**
  - Effort to prepare and submit a parent DMF (including FDA review) **~150 hours**
  - Annual effort to maintain a DMF **~75-125 hours**
  - Close coordination between DMF Owner ↔ Regulator ↔ Applicant(s)
  - Consider consultants to manage this for you
- Compliant QMS and DMF = attractive proposition to potential customers

AtomVie
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Empowering Next Generation Radiotherapeutics

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