STATEMENT OF WORK

3D Microscopy, Artificial Intelligence-based Quantification, and Modeling for Non-Clinical Evaluation and Regulatory Support of Complex Drug Products

1. Introduction

1.1. Background

The Food and Drug Administration (FDA) protests public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

The Office of Generic Drugs (OGD) within FDA is responsible for the review and approval of abbreviated new drug applications. OGD's mission is to ensure, through a scientific and regulatory progress, that generic drugs are safe and effective for the American public. The Office of Research and Standards (ORS) within OGD has been leading research efforts to facilitate generic development and approval.

The Code of Federal Regulations (CFR) Title 21 Part 7 (21CFR7) governs the practices and procedures applicable to regulatory enforcement actions initiated by the FDA pursuant to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) and other laws that it administers. A recall is a firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers.

2. Contract Type

This is a single award, Indefinite Delivery-Indefinite Quantity (IDIQ) type contract, with Firm-Fixed Price task type orders.

3. Minimum and maximum contract value

a) The minimum guarantee is $500.00.
b) The Maximum Value for this contract is $4,999,999.00.

4. Ordering

a) Any supplies and services to be furnished under this contract shall be ordered by issuance of delivery orders or task orders by the individuals or activities designated in the Schedule. Such orders may be issued from the period of performance start date of the IDIQ through five years.

b) All delivery orders or task orders are subject to the terms and conditions of this contract. In the event of conflict between a delivery order or task order and this contract, the contract shall control.

c) A request for task order proposal (RFTOP) will be issued via email. The contractor will typically have a minimum of ten (10) business days to respond to any RFTOP. Orders against that IDIQ contract will be issued via email.

d) Proposals submitted in response to a RFTOP must utilize the Ordering Period rates listed in the pricing schedule based on the performance start date of the task order, and that rate must be used for the duration of the task order performance period (not to exceed 12 months, and the performance end date cannot be more than 12 months after the IDIQ performance end date).

5. Pricing

The total amount specified in Firm-Fixed Price (FFP) task orders shall be fixed for the task order period of performance and shall not be subject to adjustment; except, as a result of a direct action or inaction by the Government which delays the Contractor from completing the task order within the time specified in the order. The Contractor shall comply with FAR Clause 52.212-4 (Contract Terms and Conditions – Commercial Items) in regard to the firm-fixed-price for the individual task orders.

Pricing Orders

a. Proposals submitted in response to a RFTOP must be in accordance with the Ordering Period rates in the IDIQ Price Schedule based on the performance start date of the task order, and that rate must be

used for the duration of the task order performance period. The Contractor may propose lower rates in response to a RFTOP.
b. RFTOPs may include option periods in accordance with FAR clause 52.217-9. However, option periods must utilize the Ordering Period rates listed in the IDIQ Price Schedule, based on the performance start date of the option period.

These Ordering Pricing terms and conditions apply to all task orders issued against this IDIQ.

During the performance period of this IDIQ, by mutual agreement of the parties, additional rates may be added to support the objectives in the SOW.

If a order's stated Period of performance must be extended as a result of Government delay, the Contractor may request that the most current labor rates be used to price the work effort during the extended period for the orders.

All orders issued hereunder are subject to the terms and conditions of this contract. This contract shall control in the event of conflict with any order.

Invoicing Instructions and Requirements
All invoicing will be in accordance with Health and Human Service Acquisition Regulation (HHSAR) Clause 352.232-71 Electronic Submission of Payment Requests (Feb 2022) and the following:

Specific invoicing instructions may be provided in each individual task order. Unless otherwise specified in the task order, the FDA Invoicing procedures are as follows:

FDA Electronic Invoicing and Payment Requirements - Invoice Processing Platform (IPP)

(a) All Invoice submissions for goods and or services must be made electronically through the U.S. Department of Treasury's Invoice Processing Platform System (IPP). http://www.ipp.gov/vendors/index.htm

(b) Invoice Submission for Payment means any request for contract financing payment or invoice payment by the Contractor. To constitute a proper invoice, the payment request must comply with the requirements identified in in FAR 32.905(b), "Content of Invoices" and the applicable Payment clause included in this contract, or the clause 52.212-4 Contract Terms and Conditions – Commercial Items included in commercial items contracts. The IPP website address is: https://www.ipp.gov.

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(1) The Agency will enroll the Contractors new to IPP. The Contractor must follow the IPP registration email instructions for enrollment to register the Collector Account for submitting invoice requests for payment. The Contractor Government Business Point of Contact (as listed in SAM) will receive Registration email from the Federal Reserve Bank of St. Louis (FRBSTL) within 3 – 5 business days of the contract award for new contracts or date of modification for existing contracts.
(2) Registration emails are sent via email from ipp.noreply@mail.eroc.twai.gov. Contractor assistance with enrollment can be obtained by contacting the IPP Production Helpdesk via email to IPPCustomerSupport@fiscal.treasury.gov or phone (866) 973-3131.
(3) The Contractor POC will receive two emails from **IPP Customer Support**, the first email contains the initial administrative IPP User ID. The second email, sent within 24 hours of receipt of the first email, contains a temporary password. You must log in with the temporary password within 30 days.
(4) If your company is already registered to use IPP, you will not be required to re-register.
(5) If the Contractor is unable to comply with the requirement to use IPP for submitting invoices for payment as authorized by HHSAR 332.7002, a written request must be submitted to the Contracting Officer to explain the circumstances that require the authorization of alternate payment procedures.

(d) Invoices that include time and materials or labor hours Line Items must include supporting documentation to (1) substantiate the number of labor hours invoiced for each labor category, and (2) substantiate material costs incurred (when applicable).

(a) Invoices that include cost-reimbursement Line Items must be submitted in a format showing expenditures for that month, as well as contract cumulative amounts.

(1) At a minimum the following cost information shall be included, in addition to supporting documentation to substantiate costs incurred.

- Direct Labor - include all persons, listing the person's name, title, number of hours worked, hourly rate, the total cost per person and a total amount for this category;
- Indirect Costs (i.e., Fringe Benefits, Overhead, General and Administrative, Other Indirects)- show rate, base and total amount;
- Consultants (if applicable) - include the name, number of days or hours worked, daily or hourly rate, and a total amount per consultant;
- Travel - include for each airplane or train trip taken the name of the traveler, date of travel, destination, the transportation costs including ground transportation shown separately and the per diem costs. Other travel costs shall also be listed;
- Subcontractors (if applicable) - include, for each subcontractor, the same data as required for the prime Contractor;
- Other Direct Costs - include a listing of all other direct charges to the contract, i.e., office supplies, telephone, duplication, postage; and
- Fee – amount as allowable in accordance with the Schedule and FAR 52.216-8 if applicable.

(b) Contractor is required to attach an invoice log addendum to each invoice which shall include, at a minimum, the following information for contract administration and reconciliation purposes:
(1) list of all invoices submitted to date under the subject award, including the following:

- invoice number, amount, & date submitted
- corresponding payment amount & date received
- total amount of all payments received to date under the subject contract or order
- and, for definitized contracts or orders only, total estimated amounts yet to be invoiced for the current, active period of performance.

(c) Payment of invoices will be made based upon acceptance by the Government of the entire task or the tangible product deliverable(s) invoiced. Payments shall be based on the Government certifying that satisfactory services were provided, and the Contractor has certified that labor charges are accurate.

(d) If the services are rejected for failure to conform to the technical requirements of the task order, or any other contractually legitimate reason, the Contractor shall not be paid, or shall be paid an amount negotiated by the CO.

(e) Payment to the Contractor will not be made for temporary work stoppage due to circumstances beyond the control of U.S. Food and Drug Administration such as acts of God, inclement weather, power outages, and results thereof, or temporary closings of facilities at which Contractor personnel are performing. This may, however, be justification for excusable delays.

(f) The Contractor agrees that the submission of an invoice to the Government for payment is a certification that the services for which the Government is being billed, have been delivered in accordance with the hours shown on the invoices, and the services are of the quality required for timely and successful completion of the effort.

(g) Questions regarding invoice payments that cannot be resolved by the IPP Helpdesk should be directed to the FDA Employee Resource and Information Center (ERIC) Helpdesk at 301-827-ERIC (3742) or toll-free 866-807-ERIC (3742); or, by email at ERIC@fda.hhs.gov. Refer to the Call-in menu options and follow the phone prompts to dial the option that corresponds to the service that's needed. All ERIC Service Now Tickets will either be responded to or resolved within 48 hours (2 business days) of being received. When emailing, please be sure to include the contract number, invoice number and date of invoice, as well as your name, phone number, and a detailed description of the issue.

6. Purpose/Objective

This contract is to develop and conduct three-dimensional (3D) correlative imaging, quantitative image analysis of CQAs, and image-based *in silico* release modeling of complex drug products. These products can include long-acting implants, microspheres, *in situ* forming depots, locally-acting topical (dermal, vaginal, rectal), transdermal, and ophthalmic drug formulations, and combination products such as inhalers. The purpose of this IDIQ contract is to provide 1) technical support to the FDA internal and external research projects that need advanced imaging characterization and image data analysis; and 2) obtain improved understanding on microstructure of various complex products and develop digital modeling tools that relate microstructure and drug release. The test samples can either be commercial products or in house formulations prepared via GDUFA funded research projects. The outcome of these studies will support the regulatory science in developing and reviewing generic drug product approval standards that will ensure safe, effective, and high-quality generic drugs are available to the public. These outcomes are aimed at providing structural characterization of complex generic products and develop models that may correlate structural characteristics with formulation performance, which provide improved understanding on the impact of formulation and manufacturing parameters on product performance. With this contract, structural characterization of these products in alignment with the goals of the FDA will be available for use by drug developers of complex generic products.

7. Scope

The contractor shall work with the FDA research team to identify complex products to be studied and provide critical technical support to FDA's internal and external research projects by conducting advance image characterization and image data analysis of identified complex products.

3D Correlative Microscopy for Drug Product Characterization

Microstructures often play a critical role in the release rate of active pharmaceutical ingredient(s) (API) from complex drug products. The encapsulation of the API dispersed or suspended inside a matrix (e.g., polymer), while providing both flexibility in drug dosing and delivery route, offers an opportunity to deliver precisely controlled release for optimal therapeutic performance. It is recognized that advanced technologies with improved resolution, faster turnaround time, and better accuracy to evaluate the critical quality attributes (CQAs) that impact drug release and performance is of critical importance. An appropriately developed method should be able to discriminate the differences in formulation composition and process variability in the manufacture of the product. 3D microscopic imaging can elucidate drug product microstructures manufactured with meaningful variations, such as particle size, drug loading, types and/or amounts of excipients, and uniformity.

Under this contract, the FDA will provide and/or direct the Contractor to obtain or purchase formulations for testing from appropriate pathway. The FDA may also provide images for further analysis in some cases. The Contractor should be able to develop and validate appropriate correlative 3D microscopy imaging methods to measure common complex drug formulations. This can include, but is not limited to, implants, intrauterine devices (IUDs), microspheres, in situ forming depots, suspensions, emulsions, gels, ointments, creams, lotions, powders, and respiratory-related dosage forms (e.g., metered dose inhalers (MDIs), dry powder inhalers (DPIs)). The Contractor should be able to select and/or develop a suitable imaging apparatus and imaging conditions relative to the dosage form being tested, including but not limited to focused ion beam scanning electron microscopy (FIB-SEM), mosaic field of view scanning electron microscopy (MFV-SEM), X-Ray microscopy (XRM), micro-computed tomography (Micro-CT), synchrotron X-ray tomography, and any combination of the previously mentioned imagine modalities in a structurally correlative design. Further, Raman microscopy, energy-dispersive X-ray spectroscopy (EDS), and mass spectroscopy imaging (MSI) such as time of flight secondary ion mass spectroscopy (ToF-SIMS) can be used in a chemical-structural correlative design.

In addition to the samples in original product form, stressed samples, aged samples, intermediately released samples (in dry or wet state), and samples with adjacent tissue (extracted from either animal or human tests) can be studied upon FDA's requests.

8. Statement of Work

This statement of work (SOW) is to conduct three dimensional (3D) correlative imaging, quantitative image analysis of critical quality attributes (CQAs), and image-based in silico release modeling of complex drug products including long-acting injectable (implants, microspheres, in situ forming depots), locally acting topical (dermal, vaginal, rectal), transdermal, and ophthalmic drug formulations, as well as drug-device combination products such as inhalers. Product and intermediate samples from the market (brand name or generic), manufactured by OGD external collaborators, or internal FDA partners will be provided to the prospective Contractor. These studies will facilitate patients' access to safe, effective, and high-quality complex generic drug products by addressing scientific questions in the development of generic drug approval standards.

The inherent complex nature of local site(s) of administration and action make formulating and assessing bioavailability of complex drug products challenging. For example, the bioavailability of an ocular implant or injectable is affected by the complex physicochemical structure of the eye and potential rapid elimination of drug via reflexive blinking, tear production, and nasolacrimal drainage. As a result, locally acting drug substances are commonly formulated in complex dosage forms such as implants, microsphere suspensions, emulsions, gels, ointments, creams, or lotions. To achieve a desirably long-acting therapeutic performance for decreased dosing frequency and improved patient adherence, a polymeric matrix is often employed. The type and amount of ingredients used as well as the manufacturing process can affect the properties of these complex dosage forms, which in turn affect the in vivo performance of the drug products.

Due to the challenges of measuring, and thus the limited data on, drug distribution in the drug product and drug release into the local tissue, there is still limited understanding of how the physicochemical properties and/or individual components of these complex formulations impact the overall bioavailability and therapeutic performance of the drug product. Thus, studies to build a fundamental understanding of how formulation properties, known as the critical quality attributes (CQAs), effect local and/or systemic bioavailability (BA) will help establish:

- A regulatory pathway for establishing quality attributes and their criticality.
- In vitro-in vivo correlation (IVIVC) or in vitro-in vivo relationship (IVIVR) models.
- The development of image-based, in-silico in vitro release test (IVRT) and/or in vitro permeation test (IVPT) methods that are sensitive and discriminatory to CQA differences.
- A reduction in generic development burden via improved data sharing and data reuse.
- The correlation to in vivo BA that will support the regulatory review and development of bioequivalence testing recommendations for these complex drug products.

Each year FDA may order a total of up to 50 sample characterizations from the following table, depending on the need for such studies and available funds. The scope of activities to be performed includes:

Types	Study	Description
I	Correlative microscopy imaging	Example imaging methods: FIB-SEM, MFV-SEM, XRM, Synchrotron NanoCT, MicroCT, EDS, Raman Microscopy, ToF-SIMS and other MSI Example type of samples: implants, microspheres, in situ forming depots, suspensions, powders, locally-acting topical (dermal, rectal, vaginal) transdermal, and ophthalmic drug formulations, and combination products such as MDIs, DPIs, and other respiratory-related dosage forms
II	AI-based CQA quantification	Size distribution, uniformity, spatial distribution of phases (API, porosity, excipients)
III	Image-based release prediction	Image-based *in silico* modelling and validation
IV	Design space of drug formulation	AI generation of potential formulations based on identified CQA (e.g.,digital drug formulations) from images of existing formulations.

FDA may order multiple studies in a single task order. With each task order, the contractor shall:

- In discussion with the FDA, develop protocol(s) for the planned study. The protocol(s) shall include at a minimum, and where applicable: Key Personnel, Background Material, Study Aims, Study Design, Sample Size Determination, Instrumentation and Analytical Sampling Procedure(s), Sampling Times and Volume, CQAs, Release Performance Predictions, Study Progress, and Adverse Event Reporting Plan.
- Perform image analysis according to FDA 21 CFR Part 11 compliance, with full audit trail available for FDA review. Document the procedure and parameters used and justify any deviations from these regulations. Analytical method validation includes all the procedures that demonstrate that a particular method used for quantitative measurement is reliable and reproducible for the intended use. The fundamental parameters for this validation include (a) accuracy, (b) precision, (c) selectivity, (d) sensitivity, (e) reproducibility and (f) stability. Incurred sample reanalysis should be performed.
- Begin study within 15 calendar days from the date the Contractor obtains approval for the protocol(s) from the COR.
- Conduct a pilot study to verify study design and analytical methodology prior to conducting the full protocol study(ies).
- Conduct basic analyses and plotting of study outcomes including, but not limited to the CQAs in section 3.3.2 and release performance in section 3.3.3. The Contractor maybe required to perform statistical analysis of the results as part of the task order.
- Provide study progress updates via regularly scheduled teleconference and/or in person meetings. Contractor shall provide a summary of the study results, details of the analytical procedures, plotted data for discussion, and tables of all raw data collected. Contractor will also prepare and submit meeting minutes to the COR no later than 5 workdays after the progress update meeting.
- Generate a final study report within 30 days of completing the study protocol for FDA review. Obtain COR approval of the final study report within 120 days of completing the study protocol. At a minimum the study report should contain: Summary, Study Aims, Background Material, Materials and Methods, Procedures, Sources of Error, Results, Protocol Deviations, Adverse Events and Concomitant Treatments, Experimental Raw Data, Amendments, and Addendums.
- Be responsible for subject recruitment, supplies, equipment, data collection, and reporting.
- Adhere to all relevant FDA guidance documents.

9. Tasks

The tasks include, but not limited to, the selection of the imaging apparatus and design, sample preparation procedure, imaging parameters, other parameters of the test method, and images with clearly annotated features.

9.1.1. AI-based CQA quantification

Correlative 3D imaging digitally transforms the drug product sample into a large number of images, that are recorded by computers in greyscale intensity per pixel. To transform greyscale values to material phase identifications, image segmentation becomes a critical step. Conventional image segmentation relies on threshold values of the intensity, which has limited success. Manual segmentation, which can be used as a last resort, is extremely time and labor consuming.

Under this contract, the Contractor will develop artificial intelligence (AI)-based models to quantify the imaging data. The imaging data can be collected by the Contractor via 1.3.1, or by the FDA and FDA collaborators. Utilizing an iterative AI method, the Contractor will start with a supervised machine learning (SML) session, where an experienced user from the Contractor, optionally in consultation with the FDA team, will teach the AI engine to recognize microstructure features based on texture, shape, and morphology. A human user will manually label and segment a set of images as “ground truths” for teaching the AI engine how to recognize the different features. A deep learning (DL) algorithm utilizing convolutional neural networks (CNNs) will then be deployed on the image datasets using the "ground truths” as a basis for evaluating the model outcome. Intermediate activations will be visualized, and manual corrections will be made to images after the final output of the algorithm to improve the “ground truth” labeling and segmentation. This will be followed by additional cycles of DL algorithms applied to the datasets. After a

sufficient number of cycles, the DL algorithms will be trained to successfully recognize features in similar images without additional supervision.

The deliverables include two scales of CQAs.

At bulk scale, the contractor will report at least one of the following,
- Density
- Uniformity
- Product dimension (or dimension distribution of particle products)

At micron scale, the contractor will report at least one of the following,
- Volume fractions of API, excipients, and porosity
- Size distributions of API, excipients, and porosity
- Spatial distribution uniformity of phases of API, excipients, and porosity

The Contractor will report the imaging and data analysis processing parameters and methods.

9.1.2. Image-based in silico release modeling

The Contractor will predict drug release performance of the samples imaged using a properly developed and validated image-based release modeling method.

The model will start with a blind prediction using only the T_0 sample images. Sensitivity of the release performance to the relevant CQAs will be conducted, upon request.

If the in vitro and/or in vivo release testing data is made available, correction models will be developed to support polymer impact, accelerated release and real time release correlations and/or IVIVCs to provide a deeper understanding how formulation properties during product development may affect the in vivo drug delivery and clearance characteristics.

9.1.3. Image-based digital drug formulation, performance prediction, and risk assessment

Under this contract, the Contractor will employ deep learning models to capture microstructure features from existing drug product samples and develop design space (e.g., digital drug formulations) to guide formulation development and assessment. The formulation parameters that can be numerically modeled include,
- Drug loading
- Drug particle size
- Drug distribution
- Porosity

9.1.4. Digital drug library

Under this contract, the Contractor will develop a drug microstructure digital library that will serve as a tool for both the FDA and generic developers to support Q3 assessments. The library will consist of the images of the drug products (from section 1.3.1), their quantified CQAs (from section 1.3.2), as well as their digital drug release modelling and formulations (from sections 1.3.3 and 1.3.4). Additional characterizations including physicochemical characterizations, and in vitro release testing (IVRT) will be stored in this digital library. Any drug sample can be added to this library, including for example RLD/reference standard (RS) products, modified-RLDs (e.g., formulation changes), generic products, stress-tested samples, digital drug formulations (from section 3.3.4), and samples in various states of in vitro/in vivo release. The Contractor will maintain this library on an FDA compliant external server, where the Contractor will be responsible for hardware, software, accessibility of the digital library, and overall maintenance of the library.

10. Contract Deliverables and Reporting

The Contractor shall provide the following, as a result of specific tasking in performance of the activities in Section 2 above:

DELIVERABLE / REPORT / DOCUMENT	Delivery Date
Submission of Study Protocol approved by COR	30 calendar days from the kick-off meeting
Submission of COR approved Bioanalytical Method Validation Report	7 - 14 calendar days prior to initiating study protocol
Presentations describing project progress	Every 6-8 weeks post COR's approval of the study protocol
Submission of technical written Reports (number depending on study duration)	120 calendar days following completion of the task order studies.

The tests to be done as appropriate include the following:

- 2D FIB SEM imaging
- 2D FIB SEM imaging analysis
- 3D FIB SEM imaging
- AI based 3D FIB-SEM quantitative analysis
- 3D FIB SEM imaging analysis
- EDS spectrum mapping
- Synchrotron X-ray imaging
- XRM uniformity analysis
- DRM density characterization
- Advanced segmentation for synchrotron
- Complex API and porosity segmentation
- Release simulation
- Permeability simulation
- AI generation of potential formulation

Reports (i.e., progress power point presentation reports, and technical written reports) containing the description of experiments, imaging results, CQA analysis, and release predictions will be provided to the FDA at defined periods. In addition, all of the raw data from the experiments will be provided to the FDA in electronic format, along with these reports. No information furnished to or generated by the Contractor in the performance of this contract will be released to the public until it has been reviewed by the COR for accuracy of factual data and interpretation. The Government will have sixty (60) calendar days after receipt of the manuscript or other written draft of the material to be released, to review, comment, and return to the contractor.

Scientific manuscripts/publications resulting from work conducted by the Contractor and Government site investigators will be prepared and published according to guidelines agreed upon at study initiation by the investigator team for that study. At study initiation, each study group shall determine the first and senior author positions. While the order of listing authors on each publication shall be determined on a case-by-case basis by mutual decision of all collaborative parties and shall reflect appropriately each author's contribution to the project, it is likely that a Contractor employee will be offered the first author position for the primary manuscript arising from the study. However, the senior author position may be offered to any member of the study team who is willing to provide substantial input into study design, implementation, and manuscript preparation and oversight of all study procedures. Study Site Principal Investigator (PI) and Principal Investigators from the other sites, including FDA, when appropriate, will be listed as authors 2-x on the manuscripts, with ordering in these positions determined by consensus based on the amount of input into the actual production of the manuscript. All authors shall provide final approval of the manuscript as written. Even though the Contractor will likely be the first author on resulting publications, it is the Government's discretion as to when the articles should be published. The Contractor shall not unduly delay publication or unilaterally decide that the data should not be published. This right is retained by the Government only.

10.1. Meetings

10.1.1. Kick-Off Meeting

The Contractor shall participate in an initial meeting with the COR; within 1 month of a receipt of a task order award. The Contractor is responsible for preparing meeting notes and providing a copy of those notes to the COR 7 calendar days after the meeting. This discussion shall include the following:

- The objectives for the Performance Work Statement,
- A high-level overview and discussion of the execution plan,
- Introduction of the Federal Contracting Officer (CO) and Contracting Officer's Representative (COR), as well as the key members of the Contractor's team,
- A high-level overview and discussion of the transition plans,
- Questions and answers regarding the engagement.

Meeting notes shall detail the discussion held at the initial meeting, capture pertinent clarifications to the scope of work, and reflect any areas of disagreement or misunderstanding on the part of either the FDA or the Contractor.

10.2 Reports

10.2.1 Study protocol and implementation plan

The Contractor shall provide a study protocol and implementation plan to the COR 30 calendar days from kick-off meeting. At a minimum the plan shall include:

- Specific Aims
- Significance
- Research Design and Methods
- Expertise
- Facilities and Other Resources
- Curriculum vitae of PI and key personnel, and if any, Co-PI(s) and collaborator(s)
- Letters of support from collaborators, if any
- Study timelines and diagrammatic representation of the proposed workflow

10.2.2 Progress PowerPoint Presentation Reports

The Contractor shall provide a presentation report to update the FDA team on the study progress every 4-6 weeks upon finalization of study protocol. At a minimum the meeting presentation shall include:

- Accomplishments/Milestones reached for each specific deliverable and/or activity for the reporting period of the contract
- General Progress on activities relating to the specific project plan
- Projected Timeline for uncompleted deliverable and/or activities based on Project Aim
- Information on any additional studies completed during the reporting period
- Information on any pending issues/concerns that are impeding completion of contract deliverables and/or activities.
- Key Personnel Report
- Any Protocol Amendments and Deviation the study protocol.

10.2.3 Technical Written Reports

The Contractor shall provide an original and electronic copy of the written technical report to the COR within 120 days following the completion of the task order studies. At a minimum the written technical report shall include:

- Accomplishments/Milestones reached for each specific deliverable and/or activity for the reporting period of the contract
- General Progress on activities relating to the specific project plan from the contract submission
- Projected Timeline for uncompleted deliverable and/or activities based on Project Aim
- General Progress on Recruitment Activities
- Information on any additional studies completed during the reporting period
- Information on any pending issues/concerns that are impeding completion of contract deliverables and/or activities.

- Key Personnel Report
- Any Protocol Amendments and Deviation the study protocol.
- The most recent institutional review board (IRB) letter and RIHSC approval letter for the study.
- Any presentation or publication material during this period
- Study Coordinator Contact Information

10.2.4 Final Report

The Contractor shall provide an electronic draft of the final report to the COR within 90 days post the expiration of the contract. The COR shall provide the Contractor comments within 60 days from receipt. The Contractor shall incorporate any comments in the final report and submit to the COR within 30 days from receipt. At a minimum the final report shall include:

Cover Page

- Contract Number and Project Title
- Project period Being Reported
- Contract Organization Name
- Author(s)
- Date of Submission

Final Report Content

- Background
- Study Aims
- Study Methods
- Study Results
- Interpretation of Study Results
- Conclusion
- Strengths of Study
- Limitations of Study
- Recommendations and Implications for Generic Drug Developments
- References
- List of Publications Posters and oral presentations (title and slides)
- Publications (reference list and articles)
- Appendices as appropriate

10.3 Final Presentation at FDA

To be determined by FDA, in consultation with the Contractor, no later than the contract expiration date. At a minimum the final presentation at FDA shall include:

- Objective of the study
- Significance of the study
- Protocol Amendments and Deviation
- Final results of the study
- Conclusion
- Strengths of Study
- Limitations of Study
- Recommendations and Implications for Generic Drug Developments

11 Inspection and Acceptance

The Government shall review all reporting requirement deliverables in accordance with specifications and standards identified in the statement of work or any directives issued by the COR. Tasks

The tasks include, but not limited to, the selection of the imaging apparatus and design, sample preparation procedure, imaging parameters, other parameters of the test method, and images with clearly annotated features.

10.1.2. AI-based CQA quantification

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Under this contract, the Contractor will develop artificial intelligence (AI)-based models to quantify the imaging data. The imaging data can be collected by the Contractor via 1.3.1, or by the FDA and FDA collaborators. Utilizing an iterative AI method, the Contractor will start with a supervised machine learning (SML) session, where an experienced user from the Contractor, optionally in consultation with the FDA team, will teach the AI engine to recognize microstructure features based on texture, shape, and morphology. A human user will manually label and segment a set of images as “ground truths” for teaching the AI engine how to recognize the different features. A deep learning (DL) algorithm utilizing convolutional neural networks (CNNs) will then be deployed on the image datasets using the "ground truths” as a basis for evaluating the model outcome. Intermediate activations will be visualized, and manual corrections will be made to images after the final output of the algorithm to improve the “ground truth” labeling and segmentation. This will be followed by additional cycles of DL algorithms applied to the datasets. After a sufficient number of cycles, the DL algorithms will be trained to successfully recognize features in similar images without additional supervision.

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The Contractor will report the imaging and data analysis processing parameters and methods.

10.1.3. Image-based in silico release modeling

The Contractor will predict drug release performance of the samples imaged using a properly developed and validated image-based release modeling method.

The model will start with a blind prediction using only the T_0 sample images. Sensitivity of the release performance to the relevant CQAs will be conducted, upon request.

If the in vitro and/or in vivo release testing data is made available, correction models will be developed to support polymer impact, accelerated release and real time release correlations and/or IVIVCs to provide a deeper understanding how formulation properties during product development may affect the in vivo drug delivery and clearance characteristics.

10.1.4. Image-based digital drug formulation, performance prediction, and risk assessment

Under this contract, the Contractor will employ deep learning models to capture microstructure features from existing drug product samples and develop design space (e.g., digital drug formulations) to guide formulation development and assessment. The formulation parameters that can be numerically modeled include,

- Drug loading
- Drug particle size
- Drug distribution

- Porosity

10.1.5. Digital drug library

Under this contract, the Contractor will develop a drug microstructure digital library that will serve as a tool for both the FDA and generic developers to support Q3 assessments. The library will consist of the images of the drug products (from section 1.3.1), their quantified CQAs (from section 1.3.2), as well as their digital drug release modelling and formulations (from sections 1.3.3 and 1.3.4). Additional characterizations including physicochemical characterizations, and in vitro release testing (IVRT) will be stored in this digital library. Any drug sample can be added to this library, including for example RLD/reference standard (RS) products, modified-RLDs (e.g., formulation changes), generic products, stress-tested samples, digital drug formulations (from section 3.3.4), and samples in various states of in vitro/in vivo release. The Contractor will maintain this library on an FDA compliant external server, where the Contractor will be responsible for hardware, software, accessibility of the digital library, and overall maintenance of the library.

Contract Deliverables and Reporting shall be submitted to the COR or government designee in accordance with the delivery schedule. The acceptance of deliverables and satisfactory work performance shall be based upon the timeliness and accuracy/quality of the deliverables.

Acceptance may be presumed unless, otherwise indicated in writing by the Contracting Officer, COR, or the duly authorized representative within 10 business days of receipt.

The Contractor shall implement necessary changes within 10 business days, or a mutually agreed upon period of time from the day of change notification.

The COR or the duly authorized representative shall perform inspection and acceptance of materials and services.

12 Location and Travel

12.2 Location

The Contractor's primary work location will be at their designated study site(s).

13 Staffing

The Contractor shall ensure that all Contractor support personnel are adequately trained, possess the requisite experience, and are otherwise fully qualified to provide the high level of support required by this SOW prior to being assigned to this contract. The Contractor shall provide the COR with an FDA EASE checklist two weeks prior to the employee's start date, unless otherwise waived by the government.