

Appendix A: RAC (US) Detailed Exam Content Outline

The RAC (US) examination is organized into four major domains, with associated tasks and responsibilities typically undertaken by a regulatory professional. The approximate distribution of types of questions for each domain is shown in the following outline. Questions on the exam will address the tasks and activities presented in this outline.

Domain I: Strategic Planning

Approximately 10 recall questions, 9 application questions, and 9 analysis questions for a 100-question examination (percent of items on exam: 28%)

- A. Regulatory Framework
 - i. Evaluate proposed products for regulatory classification (drug/device/biologic/combination/OTC/predicate devices, etc.) and jurisdiction (CDER/CDRH/CBER, etc.).
 - ii. Monitor and assess the regulatory environment (product specific guidances, competitor products, etc.) to propose regulatory path forward (generic/OTC/predicate device, etc.).
 - iii. Evaluate US regulatory implications for non-US (global) development and marketing.
 - iv. Provide input to FDA and industry (PhRMA, AdvaMed, etc.) and standards (USP, ASTM, ICH, etc.) organizations to influence the US regulatory environment (legislation, regulations, guidance documents, standards, etc.).
- B. Regulatory Pathways and Operations
 - i. Determine requirements (local, national, international) and options for regulatory submissions (NDA/BLA/PMA/510k, electronic/paper, 505(b)(2), etc.), approvals (priority review, user fees, etc.), and compliance activities (registration, listings, etc.).
 - ii. Advise management on timelines, benefits/risk assessment and financial implications of the proposed regulatory strategy.
 - iii. Investigate and communicate to management the availability of incentives (pediatric, orphan, fast track, HDE, etc.) to support product development.
 - iv. Develop optimal strategy for Agency interactions during product development and life cycle management.
 - v. Advise internal stakeholders (marketing, manufacturing, R&D, etc.) regarding current/pending guidances, regulations, Agency/industry initiatives, etc. to ensure regulatory strategy is in alignment with company objectives.
 - vi. Consult with marketing/project team to develop intended use and claims (target product profile).
 - vii. Assess quality systems (e.g., CE marking, ICH, GMP/QSR, ISO, etc.) by performing audits to determine compliance to Quality System Regulations (QSR) and Drug GMP, assuring compliance to established SOPs for QSR and drug GMPs [e.g., failure investigations, etc], and making recommendations for improvement of quality systems, based on audit findings and QSR or GMP requirements.
 - viii. Develop/deliver/assure in-house training programs for all company personnel for regulatory compliance (Refers to GXP).
 - ix. Assure implementation and documentation of training programs including identification of training needs (job-specific and general GMP training) and training schedules.
 - x. Provide trainers with updated information on regulatory requirements to incorporate in on-going training programs.
- C. Interaction With Other Companies
 - i. Conduct regulatory due diligence and advise senior management during product or company acquisitions and collaborations.
 - ii. Ensure regulatory obligations are met for in- and out-licensing of products.
 - iii. Ensure regulatory obligations are met for contract activities (manufacturing, complaint handling, regulatory operations, consultants, etc.).

Domain II: Pre-Approval

Approximately 9 recall questions, 8 application questions, and 8 analysis questions for a 100-question examination (percent of items on exam: 25%)

- A. Non-clinical Development
 - i. Determine test requirements (GLP/non-GLP, biocompatibility, carcinogenicity studies specific to drug/biologic/device, etc.) and identify applicable guidances and resources for such requirements.
 - ii. Ensure compliance with non-clinical safety requirements (GLPs) and applicable performance standards (ISO, ASTM, ANSI, ICH, etc.).
 - iii. Determine adequacy of non-clinical data and risk analysis to support initiation of clinical trials including any appropriate risk management.
 - iv. Assess quality systems (e.g., CE marking, ICH, GMP/QSR, ISO, etc.) by performing audits to determine compliance to Quality System Regulations (QSR) and Drug GMP, assuring compliance to established SOPs for QSR and drug GMPs [e.g., failure investigations, etc.], and making recommendations for improvement of quality systems, based on audit findings and QSR or GMP requirements.

- B. Clinical Development
 - i. Determine requirements with regard to clinical safety and efficacy (GCPs).
 - ii. Ensure compliance with all clinical standards (GCPs, clinical trial monitoring and auditing), IRBs, safety reporting, informed consent, financial disclosure, etc.).
 - iii. Advise project team of regulatory recommendations for ongoing aspects of clinical trials/investigations (amendments to protocol, etc.).
 - iv. Identify non-US country specific requirements for impact to US submissions (IND/IDE, annual report, etc.).
 - v. Prepare and/or review information included in IND/IDE submission such as label, clinical investigation plan/protocol, case report form, investigators brochure, informed consent, etc.
 - vi. Ensure that any identified safety risks have been appropriately addressed with the clinical development program.
 - vii. Ensure that CFR requirements for adverse event reporting are established and being followed.
 - viii. Evaluate need for and contribute to the development of Pediatric Development Plan and/or waivers/deferrals, Orphan Designation Applications, etc.

- C. CMC/Device Design and Manufacturing
 - i. Determine regulatory requirements for manufacturing /quality system certifications (clinical trial supplies, manufacture, dosage forms, device classification, DMFs, etc.).
 - ii. Ensure compliance with cGMPs and QSR (SOPs, record retention, calibration, etc.).
 - iii. Verify device Design History File complies with regulatory requirements including risk management.
 - iv. Ensure regulatory compliance of manufacture and release of investigational products for clinical use.
 - v. Review completeness of documentation to support IND/IDE submissions.
 - vi. Ensure specifications for testing of API/drug substance/drug product and documentation of raw materials (novel excipients, animal derived materials, etc.) comply with regulatory requirements.
 - vii. Ensure specifications for device components, manufacturing process, and product have been defined and meet regulatory requirements (including product and quality system software).
 - viii. Evaluate manufacturing changes for compliance with appropriate change control systems/process and determine regulatory filing strategy.
 - ix. Review and monitor regulatory compliance for suppliers (contract manufacturers, CROs, etc.).

- D. Agency Interaction
 - i. Prepare pre-market submissions (IDE/IND) and master files for drugs/biologics/devices including investigational labeling.
 - ii. Ensure that the project is in compliance regarding submission format (CTD/eCTD, etc.).
 - iii. Review application for completeness according to “refuse-to-file” guidelines.
 - iv. Negotiate/interact as appropriate with Agency during development/submission process (Pre-IDE/IND, End of Phase 2, Meetings, Respond to Agency comments, etc.).
 - v. Monitor and maintain ongoing IDE/IND applications (e.g., amendments, annual reports, updates).
 - vi. Determine requirements for export/import of investigational products (customs, USDA, etc.).
 - vii. Ensure that the identified risks have been appropriately flagged and monitored.
 - viii. Initiate process to obtain non proprietary (USAN) and proprietary names.

Domain III: Approval

Approximately 8 recall questions, 8 application questions, and 8 analysis questions for a 100-question examination (percent of items on exam: 24%)

- A. Non-clinical Section
 - i. Assess and verify adequacy of non-clinical data to support approval.
 - ii. Assemble non-clinical reports and prepare non-clinical summary documentation as appropriate.
- B. Clinical Section
 - i. Assess and verify the adequacy of clinical safety and efficacy data to support approval and desired label claims.
 - ii. Assemble clinical reports submission and prepare summary documentation as appropriate.
 - iii. Ensure clinical trial monitoring and clinical trial audits are performed and documented.
- C. CMC/Device Design and Manufacturing
 - i. Assess and verify the adequacy of data to support submission approval and desired label claims/product specifications.
 - ii. Assess and verify the readiness of the drug/device manufacturing facility for PAI (Ensure compliance with GMP and QSR).
 - iii. Assemble CMC documentation for submission and prepare summary documentation as appropriate.
- D. Submission and Review Process
 - i. Prepare and schedule pre-submission meetings with the Agency at the appropriate stage of the submission (e.g., pre-IND/IDE, end of Phase 2, etc) to reach agreement on content, format, and other issues/proposals.
 - ii. Guide project regarding submission format (CTD/eCTD, paper, etc.).
 - iii. Negotiate/interact as appropriate with Agency during the submission process (120 Day Safety Report, Respond to Agency comments, 100 Day Review, etc.).
 - iv. Prepare for and participate in Advisory Committee Meeting/Advisory Panel Meeting if requested.
 - v. Drive the creation of draft labeling that meets regulatory requirements and negotiate final labeling with FDA at end of review period (SPL).
 - vi. Develop post approval regulatory plans and negotiate agreement with FDA (e.g., risk evaluation and mitigation strategy (REMS) and post market clinical follow up plan).
 - vii. Provide guidance to project teams on FDA review practices and current thinking (refusal to file, priority review assignment, FDA's Best Review Practices, etc.).

Domain IV: Post-Approval

Approximately 8 recall Questions, 8 application questions, and 7 analysis questions for a 100-question examination (percent of items on exam: 23%)

- A. Postmarketing/Maintenance
 - i. Submit required licensing fees, drug and device listings, periodic reports and updates (e.g., PSURS, master files, etc.).
 - ii. Comply with product post-marketing approval requirements/condition of approval studies (Phase IV Studies).
 - iii. Prepare, implement and monitor strategy for alerts/notifications/recalls/market withdrawal.
 - iv. Advise management on alerts/notifications/recalls.
 - v. Provide regulatory input on post-approval change management.
 - vi. Assess documentation to support product and process changes and determine regulatory category of change (PAS, CBE, Annual Reports, etc).
 - vii. Prepare and submit supplements/design change applications and notifications to NDA, BLA, PMA.
 - viii. Maintain and record changes to the technical file/design dossier or NDA/BLA.
 - ix. Ensure compliance with Risk Evaluation and Mitigation Strategy (REMS).
- B. Postmarketing Surveillance/Vigilance
 - i. Evaluate reports of product complaints.
 - ii. Ensure that appropriate systems are in place to document and track product complaints and ADR reports.
 - iii. Ensure implementation of necessary corrective actions based on results of inspections, audits, failure analysis and consent decrees.
 - iv. Report product safety issues/failures to regulatory agencies as required [e.g., ADEs].
 - v. Review adverse drug reaction reports and medical device reports.

- C. Advertising/Promoting/Labelling
 - i. Review and approve revised labelling and claims, public communications, press releases, advertising, and promotional items for regulatory compliance.
 - ii. Evaluate data to support comparative claims in advertising and implications of off-label use.
- D. Distribution
 - i. Ensure compliance with regulatory requirements for supply, handling, storage, distribution, import, and export of materials.
 - ii. Ensure compliance with applicable requirements/regulations for distribution of controlled substances.
 - iii. Review regulatory aspects of contracts for product distribution (e.g., product complaints, product tracking, etc.).
 - iv. Advise on the issues related to drug/product/lot releases (Annual Product Review, Device History Record).
- E. Crisis Management
 - i. Advise management regarding the regulatory impact of a crisis event.
 - ii. Develop regulatory plan to address the crisis event.
 - iii. Advise management on regulatory implications of proposed crisis resolution strategies.
- F. Agency Interaction
 - i. Facilitate coordination of outside consultants and company personnel in response to Agency comments (PAI, 483 responses, conduct of clinical studies, etc.).
 - ii. Negotiate with Agency wording of inspection findings.
 - iii. Manage/accompany/chaperone inspection teams or auditors.
 - iv. Advise internal functional groups regarding regulatory compliance (e.g., FDA 483's, warning letters, and consent decrees) and communicate corrective follow-up actions to management.
 - v. Prepare strategy/briefing documents for panel hearings and informational meetings (Advisory Committee).
 - vi. Communicate/refer external requests for information.
 - vii. Develop Freedom of Information Act strategy regarding confidentiality and protection of proprietary information and document requests.