



From Bench to FDA: Career Development Outside of the Laboratory

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Outline

- Introduction
 - Drug Development overview
 - Pharmaceutical Quality
- CDER Regulatory Applications
 - Investigational New Drugs (INDs)
 - New Drug Applications (NDAs)
- A day in the life...
- Skill sets – from here to there?
- General thoughts
 - Questions
- Conclusions



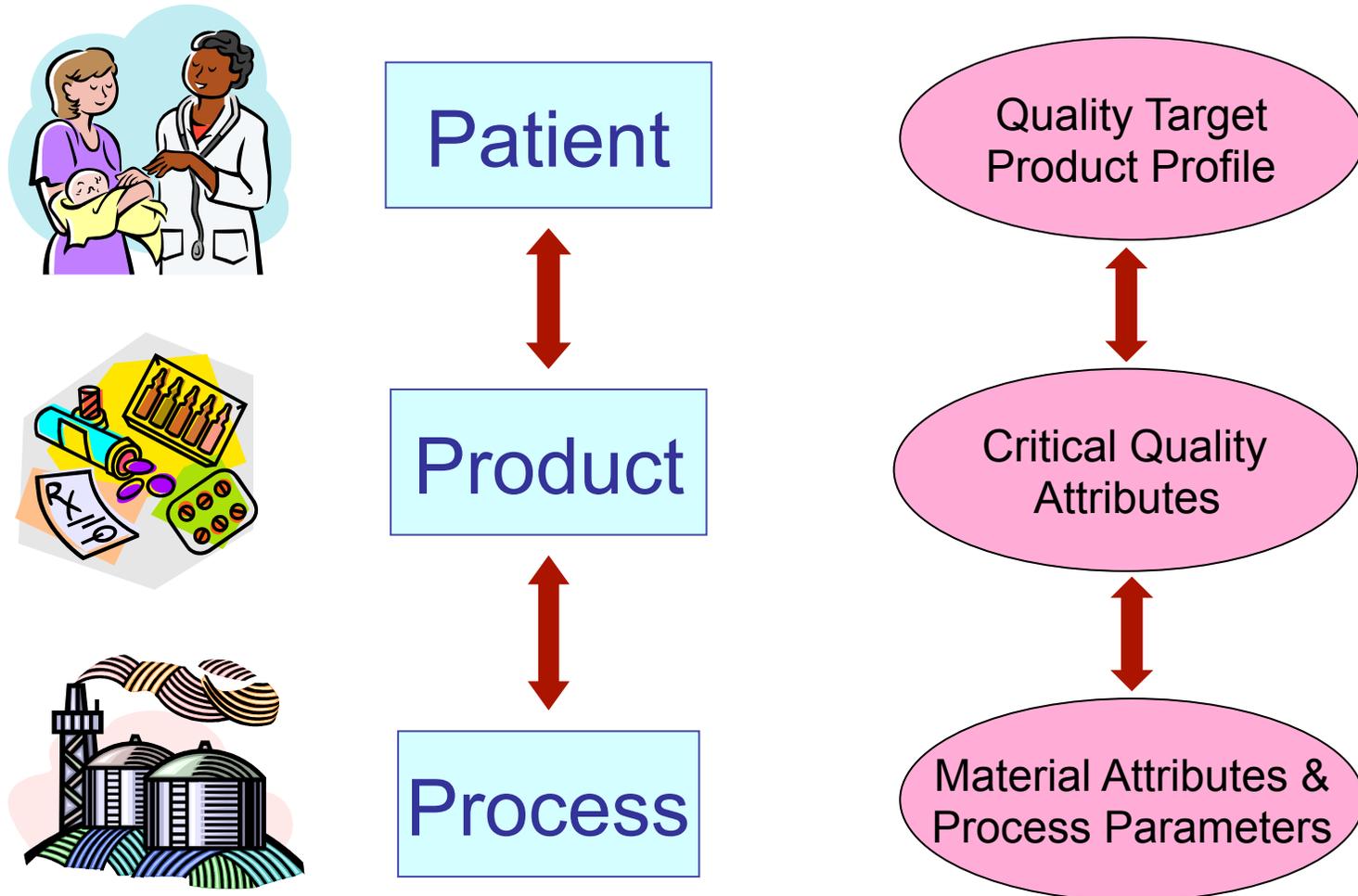
Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe
- Are efficacious
- Have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed



Linking Process - Product - Patient





Why is Quality Important?

- Ties product performance to label claim
- Applies to design, manufacture and clinical use of product
- Relates critical attributes of the drug to patient safety and fitness for use
- Necessary for product availability to patient (i.e., poor quality often results in recalls and shortages)



CDER Regulatory Submissions

Investigational New Drugs (INDs)

- First in human studies
- “Commercial” and “Research”
- Treatment protocols
- Single patient INDs

New Drug Applications (NDAs)

- Original NDA submissions
- Priority vs standard designations
- “Breakthrough Therapies”



Agency Meetings/Interactions

- PreIND
- EOP1
- EOP2
- preNDA
- Others as required
- Terminology (Sponsor, Applicant)

Everything tracked officially (DARRTS)
For every meeting, there are two meetings!



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IND Submission and Review Process



IND Submissions

Initial INDs

- 30 day evaluation period
- Focus on safety
- Safe to proceed or clinical hold
- Some Sponsors elect to withdraw or inactivate rather than be placed on clinical hold
- Some considerations
 - Patient population
 - Dosage form
 - New molecular entity
 - Manufacturing process



IND Submissions – Regulations

21 CFR 312.23(a)(7)(i)

“Sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug.”

“...the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available.”



IND Clinical Holds – Regulations

21 CFR 312.42

- Order by the FDA to suspend or delay a clinical investigation
- Proposed studies may not proceed

21 CFR 312.42(b)(iv)

“The IND does not contain sufficient information required under § 312.23 to assess the risks to subjects of the proposed studies.”



IND Guidances

- INDs for Phase 2 and Phase 3 Studies
Chemistry, Manufacturing, and Controls (CMC)
Information
- Content and Format of Investigational New Drug
Applications for Phase 1 Studies of Drugs
- Apply to both research and commercial sponsors
of INDs



The Initial IND Submission

IND Submission (21 CFR 312)

- Goal: Develop data in humans for submission of an NDA
- Components
 - Cover sheet (21 CFR §312.23(a)(1))
 - Table of contents (21 CFR §312.23(a)(2))
 - Introductory statement and general investigational plan (21 CFR §312.23(a)(3))
 - Brief 2-3 page summary
 - Helps FDA anticipate sponsor needs



The Initial IND Submission (continued)

- Investigator's brochure(21 CFR §312.23(a)(5))
 - Compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects
 - Facilitates investigator understanding of rationale of key features of the protocol (dose frequency/ interval, methods of administration)
- Protocols (21 CFR §312.23(a)(6))
- Chemistry, Manufacturing, and Control (CMC) information (21 CFR §312.23(a)(7))
 - Information on drug substance and drug product



The Initial IND Submission (continued)

- Pharm/Tox studies (21 CFR §312.23(a)(8))
 - Description of pharmacological effects, ADME
 - Integrated summary of toxicological effects in animals and *in vitro* studies
 - » Study reports should be available to FDA within 120 days of the start of the human study
- Previous experience (21 CFR §312.23(a)(9))
 - presented in an integrated summary



The IND Review Team

- Primary Clinical reviewer
- Primary Chemistry reviewer
- Primary PharmTox reviewer
- Sometimes: Clinical Pharm., Microbiology, Biopharmaceutics
- Project manager
- Supervisory/secondary signoffs



Initial INDs: The Safety Determination

Two possibilities

- FDA inaction in 30 days triggers proposed clinical studies – safe to proceed
- FDA issuance of “clinical hold” – no clinical studies can be conducted

If a study is not determined to be safe to proceed, the IND is placed on “clinical hold.”



IND “Safety Issues”

- Safety issue = a scientific issue which requires data and/or resolution prior to the initiation of the proposed clinical trial(s).
- Attempt to resolve all IND safety issues prior to 30-day “safety date”.
- Unresolved safety issues result in a recommendation for a clinical hold.



Examples of CMC “Safety Issues”

- Lack of batch analysis (preclinical and/or clinical)
- Insufficient or missing compatibility data
- Inconsistent or deficient CMC information
- Lack of detail regarding manufacturing process
- Lack of sterility assurance
- Lack of proper authorization for cross-referenced information
- Omission of CFR-required CMC items



IND Safety Reviews – Process

During IND safety review (30 days), the CMC reviewer:

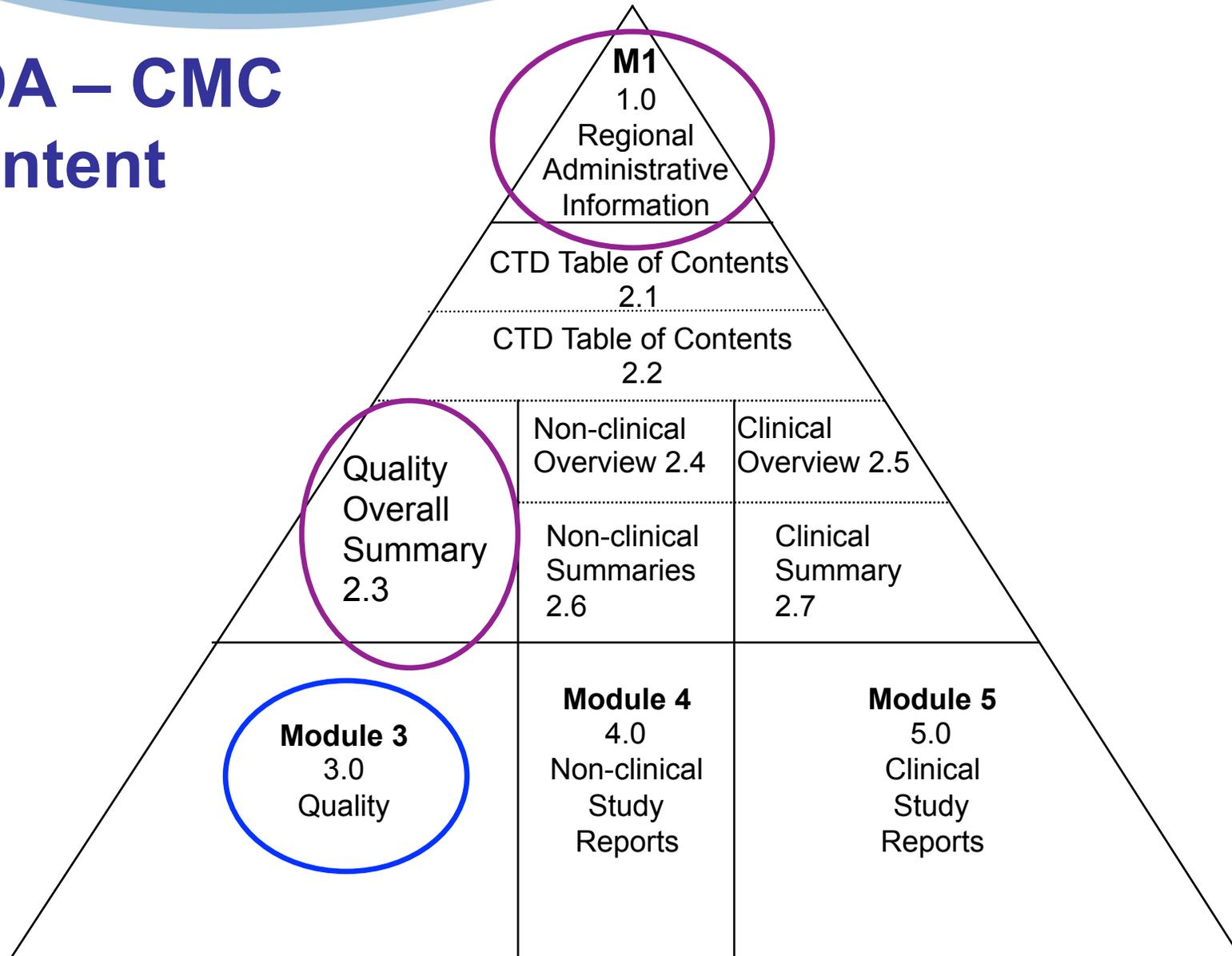
- Confirms required CMC information
- Develops a CMC safety recommendation of “safe to proceed” or “not safe to proceed”
- Documents with written review
- Conveys/discusses recommendation to multidisciplinary team



NDA Submission and Review Process



NDA – CMC Content





The NDA Primary Review Team

- Medical Officer
- CMC Reviewer
 - Biopharmaceutics Reviewer as needed
 - Use of team review
- Statistics Reviewer
- Clinical Pharmacology Reviewer
- Pharmacology/Toxicology Reviewer
- Project Manager(s)
- Supervisory signoffs for all disciplines
- Consults: Microbiology, others as needed



The Complete NDA Submission

Application content and organization (21 CFR 314.50)

1) Index

2) Labeling

- Draft container labels
- “Patient package inserts” (PPIs)

3) Application summary

- Statement on pharmacologic class, clinical benefits, and scientific rationale
- CMC information
- Foreign marketing history



The Complete NDA Submission (cont.)

4) Chemistry

- Drug substance
 - Physical & chemical characteristics
 - Manufacturer name & address
 - Synthesis and control methods
 - Stability data
- Drug product
 - Components & composition
 - Batch production records
 - Master production record (21 CFR § 314.420)
 - Manufacturing and packaging procedures
- Environmental assessment
- Methods validation package



The Complete NDA Submission (cont.)

- 5) non-clinical pharmacological and toxicological information
- 6) human pharmacokinetic (PK) and bioavailability information
- 7) microbiology
- 8) clinical information
- 9) safety update
- 10) statistical information
- 11) case report tabulations
- 12) case report form submission



The Complete NDA Submission (cont.)

- 13) patent & exclusivity information
- 14) establishment description
 - Description of manufacturing facilities
- 15) debarment certification
 - Statement confirming that no debarred individual's services were used in connection with the NDA
- 16) field copy certification
 - Statement confirming that a true copy of the chemistry section was submitted to the applicant's home district office
- 17) user fee cover sheet
- 18) miscellaneous (i.e. financial disclosure)



The NDA Review (Legislation)

User fees -- “Prescription Drug User Fee Act” (PDUFA)

- 1992: Fees used to reduce the time required to evaluate certain human drug applications without compromising review quality
- 1997(PDUFA II)
 - Reauthorized as part of FDAMA through Sept. 30, 2002
 - Phased in over five years
 - Review times dropped from 1993 to 1997 from 20 months to 12 months
- 2001/2002 (PDUFA III)
- 2007 (PDUFA IV, FDAAA)
- 2012 (PDUFA V, FDASIA)



During the NDA Review...

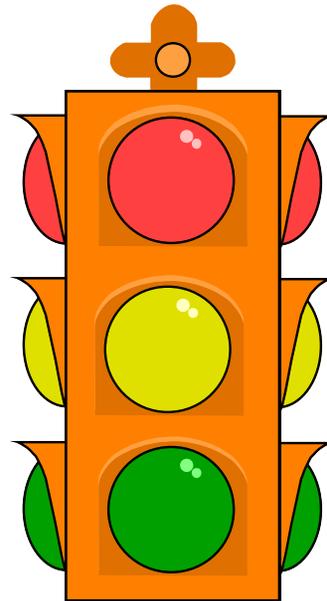
- Pre-approval inspections/cGMP evaluation
- Information requests to Applicant
- Teleconferences as necessary
- Responses sent to Agency for review
 - Timely submissions expected
 - Submissions often governed by previous agreements
 - Submissions received in last 3 months of review clock – possibly considered MAJOR amendments
- Advisory committees (NMEs)
- Labeling review, including container/carton
- Decision on approvability by action due date



NDA Actions

Approval

Complete Response





NDA Reviews – Process

During an NDA review, the CMC reviewer:

- Confirms required CMC information
- Develops a CMC recommendation of “Approval” or “Complete Response”
- Documents with written review
- Conveys/discusses recommendation to multidisciplinary team



Information Contained in Action Letter

- Outstanding deficiencies, if any
- Sites receiving withhold recommendations
- Expiration dating period for approvals
- Full labeling, including container/carton labels, for approvals
- Post-marketing studies, as appropriate
- Input from all disciplines – signed off by clinical division or office



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From Bench to FDA...



A Day in the Life

- Primary reviewer
 - Detailed analysis of submitted data/information
 - Multidisciplinary interactions, presentations
 - Lots of writing and discussing
 - Lots of desk work with meetings and overlapping deadlines
- Lead
 - Works routinely with review teams
 - Works with primary reviewers as needed
 - Multidisciplinary interactions, writing, etc
 - Speaks for discipline in many meetings



A Day in the Life

- Branch Chief, Division Director, etc
 - Member of management, handles personnel issues
 - Secondary reviews for primary reviewers
 - Policy involvement
 - Heavy communication and interaction
 - Schedule constraints due to frequent meetings
 - Higher level of access, frequent external presentations
 - Straight leadership at senior levels
 - Establishes vision for the organization at senior levels



From Here to There – How?

- What do I like to do?
- What are my strengths?
- What do I want to develop?
- What are my areas for improvement?
- What kind of career path do I prefer?
- How do I want to work?
- Think BIG...



What Worked for Me...

- Cast a big net (~90 resumes)
- Developed a CV and a resume
 - Unique cover letter for each application
- Used specific resumes for specific paths
- Interfaced regularly with NIDA advisor
- All ideas welcome
- References established early
- Reached out to connections



General Thoughts - Transitions

- Everyone starts somewhere
- Bench/research experience remains critical even in a non-research career
- Sell your ability to learn
- Writing, collaborating on interdisciplinary teams, communicating...all valuable skills
- Explore outside of your “comfort zone”
- Don’t be afraid to be practical



General Thoughts - Interviews

- Stay curious
- Prepare
- Explore any possible avenues
- Remember that the job is not just the position description
- Arm yourself with meaningful questions
- When speaking to groups, view them as potential colleagues



General Thoughts - Interviews

- Tie other interests to your career
- Use as an opportunity for information
- Practice your presentation
- Always remain courteous
 - Thank you notes, acknowledgements
 - Watch your airtime
- Pin down the follow up at the interview
 - Timing
 - POC
 - On your end?



Concluding Thoughts

- Everyone started somewhere (ask!)
- Not all technical positions require technical (bench) prowess
- Marketable skills can come from many sources
- In interviews, people may be asking “Do I want to work with this person?”
- If you are pursuing a non-bench career, don’t discount your bench experience
- Stay one step ahead
- Build connections wherever possible



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Thank you!