Hot Topics - Drug Substance Review in CDER

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OFFICE OF PHARMACEUTICAL QUALITY

Outline

- An introduction to the Office of New Drug Products (ONDP)
  - Division of New Drug API
  - Division of Lifecycle API
- ONDP Drug Substance Operational Update
- ONDP Drug Substance Review Initiatives
- Starting Material Selection

Office of Pharmaceutical Quality (OPQ)

- Organization stood up on January 11, 2015.
- Combined components of the former CDER Office of Pharmaceutical Science (OPS) and CDER Office of Compliance
- Expected to provide better alignment among all drug quality functions at CDER, including review, inspection, and research.

CDER OPQ

- Focus areas for new office:
  - Integrated approaches for review and inspection
  - Risk based approaches to review and inspection
  - Modern regulatory science approaches (e.g.,clinically relevant specifications, etc.)
  - Implement a lifecycle approach to quality
  - Improve data management and surveillance

THE OFFICE OF PHARMACEUTICAL QUALITY

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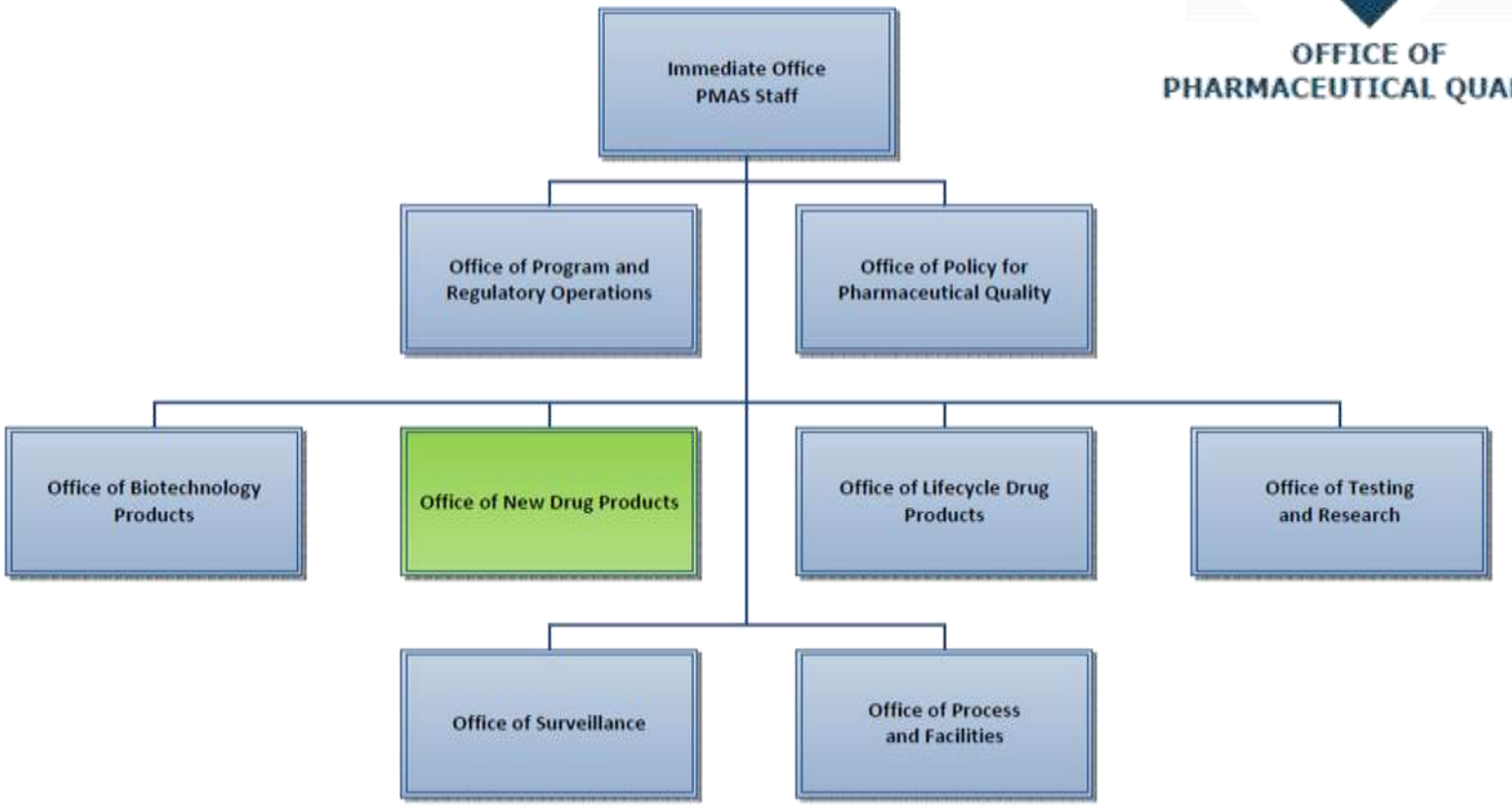
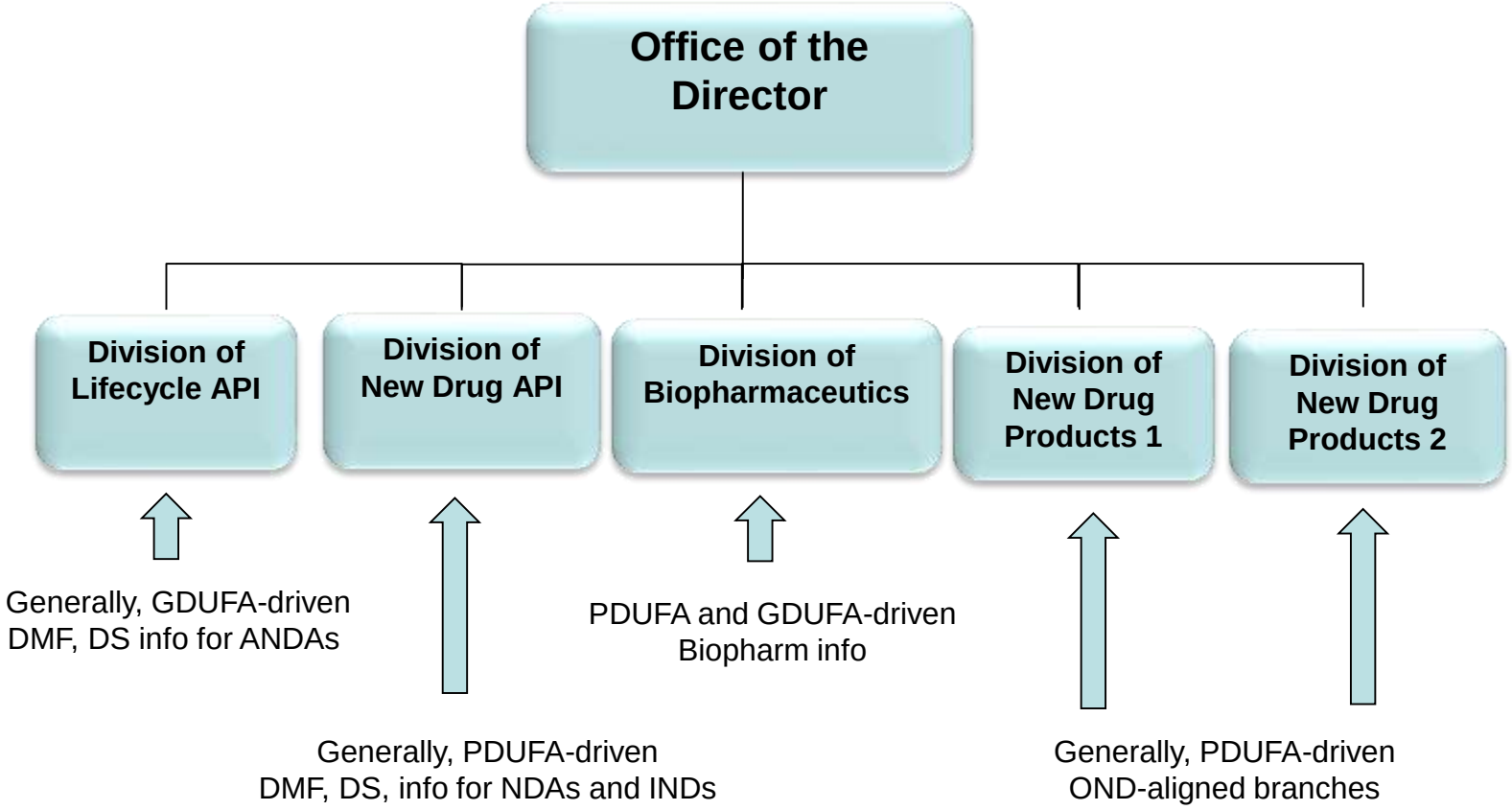


Office of New Drug Products (ONDP)



ONDP Drug Substance Operational Update

- Lifecycle API
  - Continuing the new OPQ integrated review model
- New Drug API
  - Mastering the new OPQ integrated review model
  - NDA Assignments under the new OPQ model started December 2014
- Opportunities for workload backfill, in both directions (i.e., New Drugs to Lifecycle and vice-versa)

ONDP Drug Substance Major Review Initiatives

- Construction of a more formalized drug substance risk assessment platform for NDAs/ANDAs
  - Building on Lifecycle API's RBR platform
- ONDP Drug Substance CHOP Team
  - Devised a new review template that will facilitate the most efficient and concise assessment of drug substance quality.
- Leveraging staff knowledge (*e.g.*, IND training of Lifecycle API staff)
- Continue support of Starting Material selection criteria

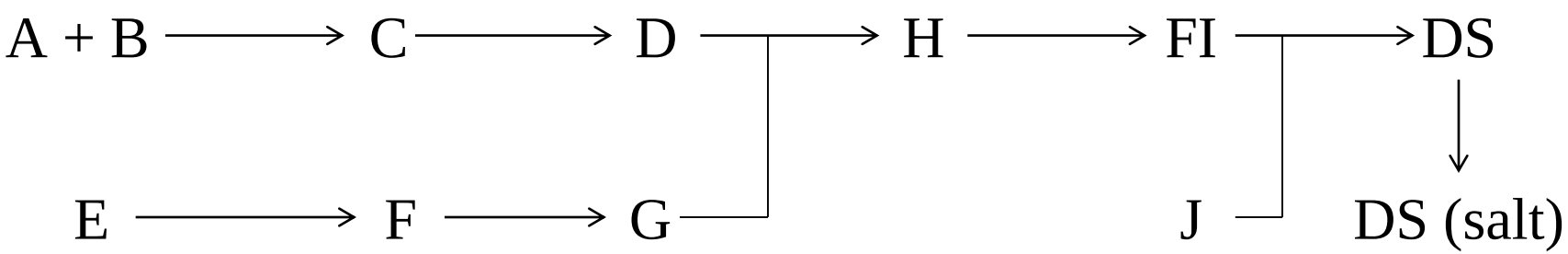
Digression: What *Are* Starting Materials?

- Arguably, the issue of starting materials is a *regulatory* question, not a *scientific* question
  - The law and regulations require that applicants describe how the drug substance is made
  - For a multi-step process, it is legitimate to ask where does the (FDA-regulated) process really "begin"
  - Chicken or egg (yin yang) of starting materials:
    - "This is where the drug substance manufacturing process 'begins,' so these must be the 'starting materials.'"
    - "These are the 'starting materials,' so this must be where the drug substance manufacturing process 'begins.'"

Applicant's Tendency

reduce costly GMP manufacture
reduce reporting of process
increase flexibility of process and sourcing

move SM forward



keep more steps reportable

Agency's Tendency

control impurities (from SM; from subsequent steps)
ensure identity of drug substance

Definition of SM Beginning with the 1987 DS Guideline

"What constitutes the starting material may not always be obvious."

- Contributes important structural element to DS
- Commercially available
- "Well-defined" in the chemical literature

Definition of SM in ICH Q7A

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

ICH Q11 SM Selection Principles

- Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate
- To conduct this assessment, enough of the drug substance manufacturing process should be described in the application
- This will typically include a description of multiple chemical transformation steps

ICH Q11 SM Selection Principles

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to have an impact on the quality of the drug substance.
- Clarification:
  - The less likely that changes to a manufacturing step can affect drug substance quality, the less reason there is for regulators to need to know about it
  - Regulators should restrain their insatiable curiosity

ICH Q11 Starting Material Principles

- Manufacturing steps that have an impact on the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application.
- Clarification:
  - If an impurity present in the drug substance arises from a certain step, changes to that step are likely to affect the amount of the impurity; therefore….
  - That step is of regulatory interest and the starting material should usually be before that step

ICH Q11 - Starting Material Principles

- Other principles:
  - Each branch of a convergent drug substance manufacturing process begins with one or more starting materials.
  - The GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material.
  - A starting material should be a substance of defined chemical properties and structure. (No non-isolated intermediates.)
  - A starting material is incorporated as a significant structural fragment into the structure of the drug substance.
- All the general principles should be considered in selecting Starting Material(s), rather than strictly applying each general principle in isolation.

Definition of SM in ICH Q7A & Q11

- More inclusive statements
  - Defines what *may* be a SM
  - Not how to select the SM(s) for a synthesis from the raw materials, intermediates, etc.
- Supports determination of SM as part of application review process

What would be ideal for SM Selection?

- General criteria/approach would be valuable
  - uniform approach across NDAs/ANDAs
  - currently: case-by-case
- Three main considerations:
  - how much of the synthesis to “report?”
  - how complex can the SM be?
  - what specification is appropriate for the SM?

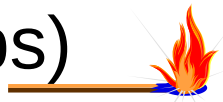
Approach to SMs in Withdrawn Draft 2004 DS Guidance

- Selection Criteria
  - Carryover of impurities into DS
  - Propinquity (# of steps)

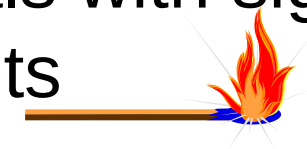
  } Properties of Synthesis

  - Isolated and purified substances
  - Complexity of Structure

  } Properties of SM



- Exception for chemicals with significant non-pharmaceutical markets



Propinquity - Assessing the Reported Portion of the Synthesis

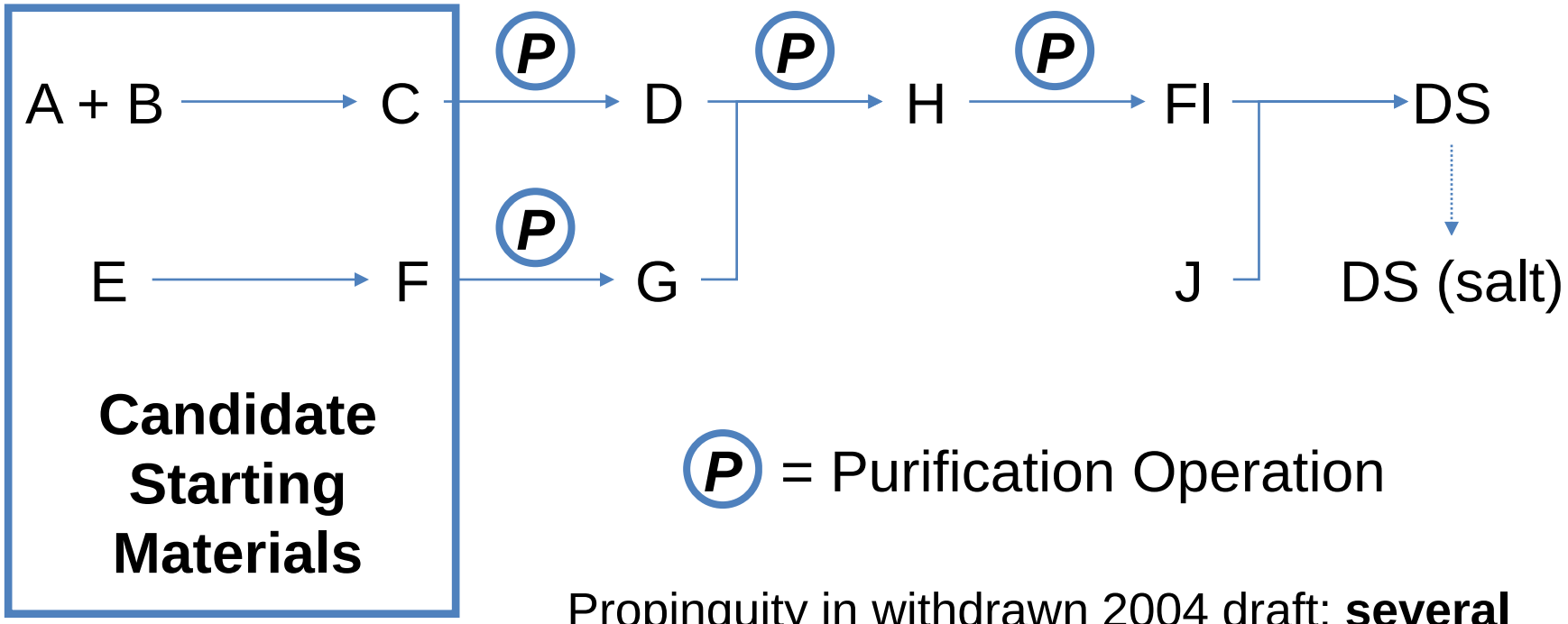
Will it be a good "Insulator?"

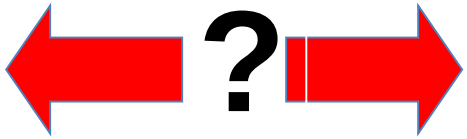
Are there a reasonable number of purification steps?

- What is a reasonable number? Counting from DS or FI?
- Count all purifications equally? Crystallization vs extractive work-up vs solvent evaporation
- Keep a reasonable amount of final synthetic steps under change control (solvents, reagents, process controls)

"Propinquity" (proximity; nearness)
A starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates.

Propinquity – Withdrawn 2004 Guidance





Propinquity in withdrawn 2004 draft: **several** reaction steps with purifications that result in isolated and purified intermediates

Points to Consider in Establishing SMs

- Final Intermediate not acceptable as starting material. Starting material should be usually be separated from drug substance by two or more synthetic steps.
- Conversion to a salt or purification of a material by conventional means does not count as a synthetic step.
- Any changes to raw materials or synthetic methods, before the designated starting material is isolated, will not have impact upon the drug substance.

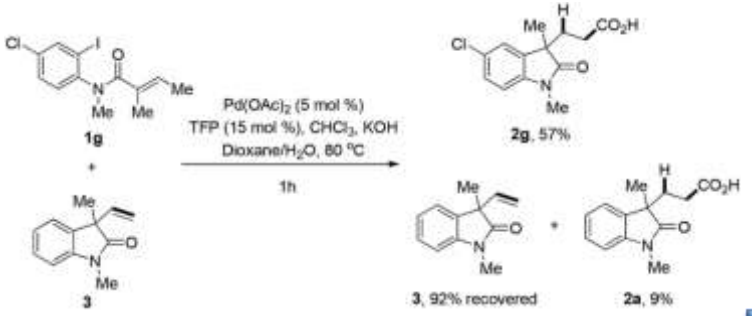
Points to Consider in Establishing SMs

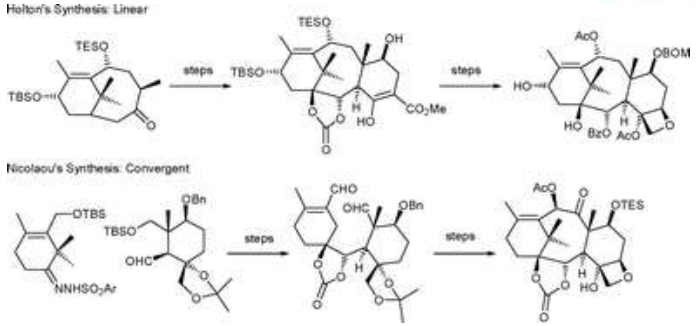
- Characterization of the designated starting material should be unambiguous
- Steps that impact the impurity profile of the DS should normally be described in the application
- Commercial Availability is less useful as a selection criterion

ICH Q11 – Recent Developments

- Drafting a Q11 Q&A Guidance Document – in progress
- Recent conversations focused on the following selection principle: "…enough of the drug substance manufacturing process should be described in the application." What does enough mean?
  - Strong Pharmaceutical Quality System (PQS), SM specification, etc. can mitigate these risks

Selection of Drug Substance SMs





Industry → ↓ ← *FDA*

How does it link to the patient?

Thank You

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