

Candidate Nomination to GMP API Supplies





Topics to be Discussed

- Development and Risk Investment Strategies
- Technical Issues/Strategies
- Drug Substance Demand/Supply Planning
- Quality Criteria/Management Strategies
- Sourcing
- Regulatory Strategy/Issues



Development and Risk Investment Strategy

- Development Strategy
 - Needs to be tailored to:
 - Internal Capabilities
 - Competitive environment
 - Lead or backup candidate
 - Priority in Portfolio of Development Candidates
 - Risk Investment Strategy
 - Impacted by:
 - Specific needs of each candidate and
 - Speed vs. staged development plan



Development and Risk Investment Strategy

- Development Strategy
 - Speed is primary driver (the majority of the time)
 - CAUTION:
 - Speed with errors always takes longer than careful work and good execution
- Risk Investment Strategy
 - Technology fit for purpose
 - Attrition is real, thus
 - Investment in technology and materials should be tailored to stage of development
 - For a given candidate, best investment strategy will be driven by:
 - technology challenges
 - development strategy
 - priority of candidate in portfolio



Development Activities – Apply to All Candidates – Synthetic and Biologics

- Technology
 - Manufacturing **AND** Analytical Technology
 - DS Form
- DS Demand, Supply, Timing
- Quality
 - Purity profile and qualification of impurities
 - Control Strategy for:
 - Genotoxic Impurities
 - Metal residues
 - Residual solvents
- Manufacturing Strategy
 - Sourcing Strategy
- Regulatory filing approach for IND



Synthetic vs. Biologic Drug Candidate

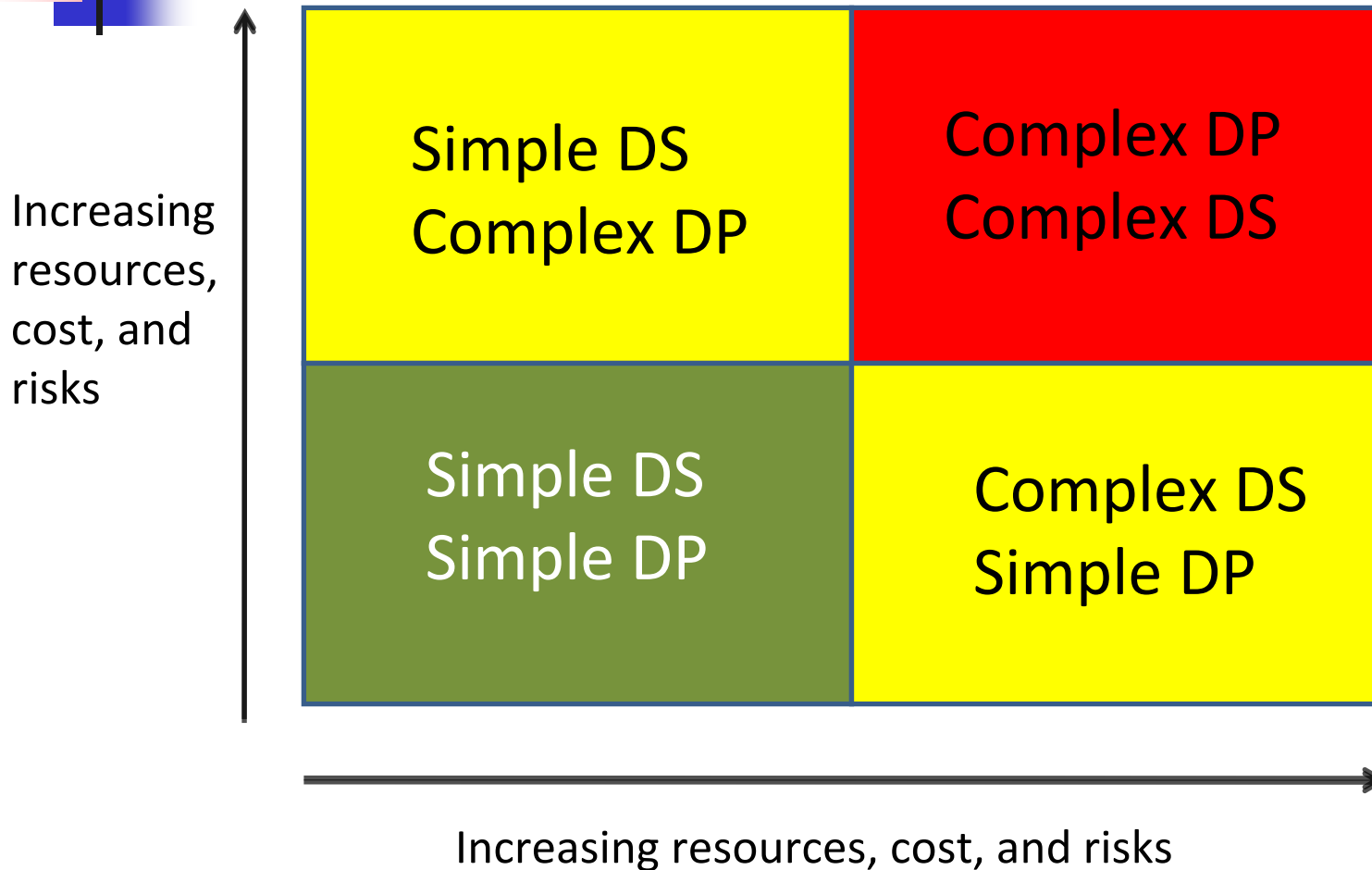
- Focus for presentation will be synthetic molecules
 - But issues are similar for biologic candidates (previous slide)
 - Major Difference
 - Biologic molecules are *product-by-process*
 - Cell line changes and/or process changes can impact biological activity



Technical Issues/Strategies

- Not all candidates created equal
 - Complexity of candidates varies considerably
 - Impacts:
 - Risks
 - Resource requirements
 - Development strategies

Complexity – Drug Candidate



Complexity – A Comparison

Synthetic Molecule DS Focus

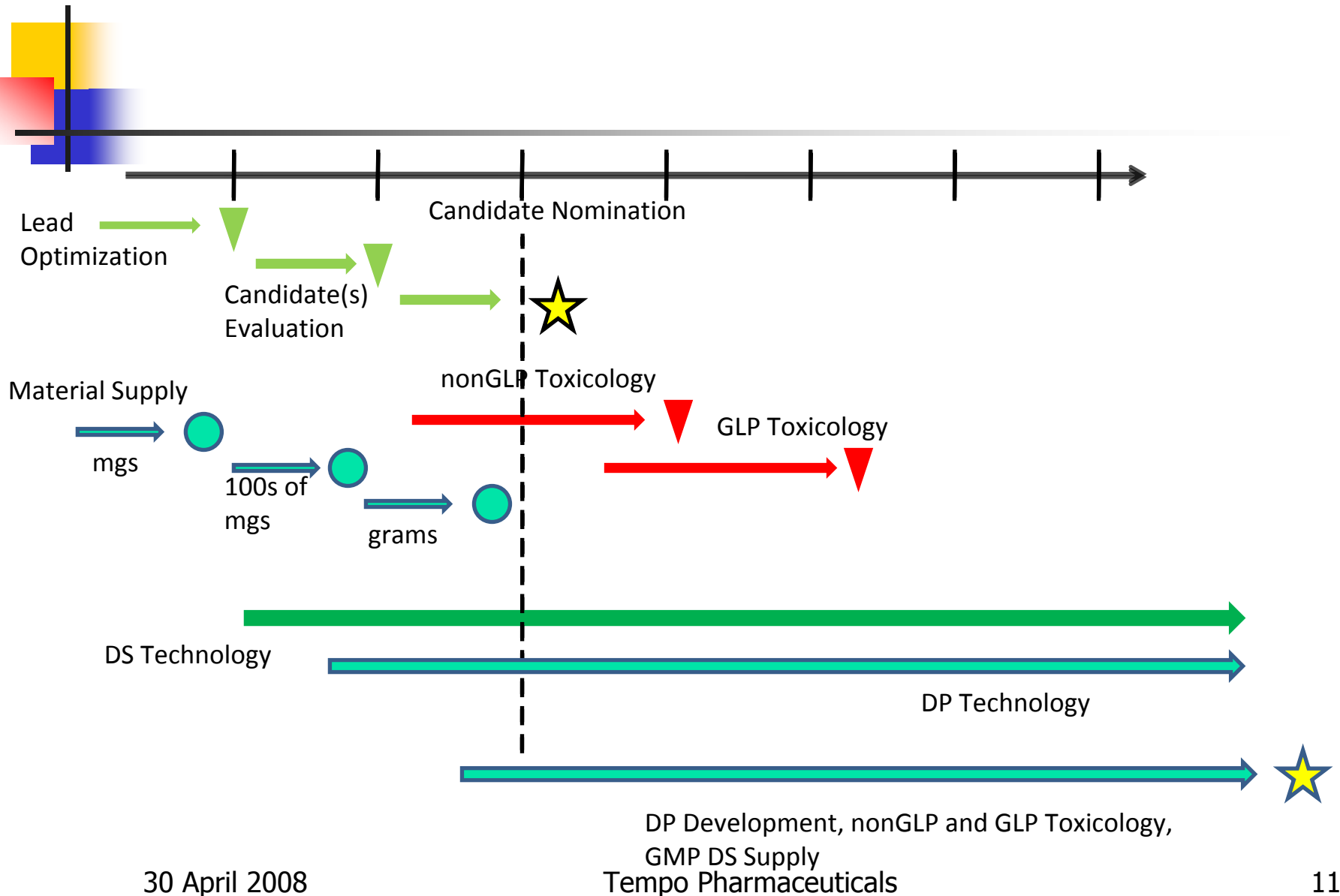
Attribute	Simple	Complex
DS Synthesis		
Length of synthesis	4 steps	20 steps
Hazardous Reagents/intermediates	None	Several
Chiral Centers	None	3
DS Physical and Toxicological Properties		
Occupational Exposure Limit	>10 ug/m ³	< 10 ug/m ³
Stability	Stable	Sensitive
Aqueous Solubility	Very Good (> 10 mg/ml)	Very Poor (<1 ug/ml)
Solid Form	Crystalline	Non-crystalline
Projected Human Dose/day	<10 mg	>500 mg



Development Partners

- Integration of planning and execution of work supported and impacted by many partners
- The Partners
 - Medicinal Chemistry
 - And biology
 - DSD/ADME
 - Drug Product Development
 - Analytical Chemistry
 - Sourcing Partners
 - Raw Material Suppliers

Integrated Planning





Integrated Development Activity - Summary

- Candidate Nomination
 - Is not a clear ending or starting point
 - Activities required to progress a candidate can:
 - Be initiated before nomination
 - Development focus
 - Material supply and technology
 - Drug delivery support for animals
 - Continue after nomination
 - Discovery focus and biological characterization of candidate
 - Development focus and related activities



Drug Substance Synthesis Technology

- First Priority
 - Near term strategy
 - Determine if Discovery process is suitable for initial quantities
 - Then determine if process is suitable for use to prepare material for GLP safety studies and clinical supplies



DS Synthesis Technology

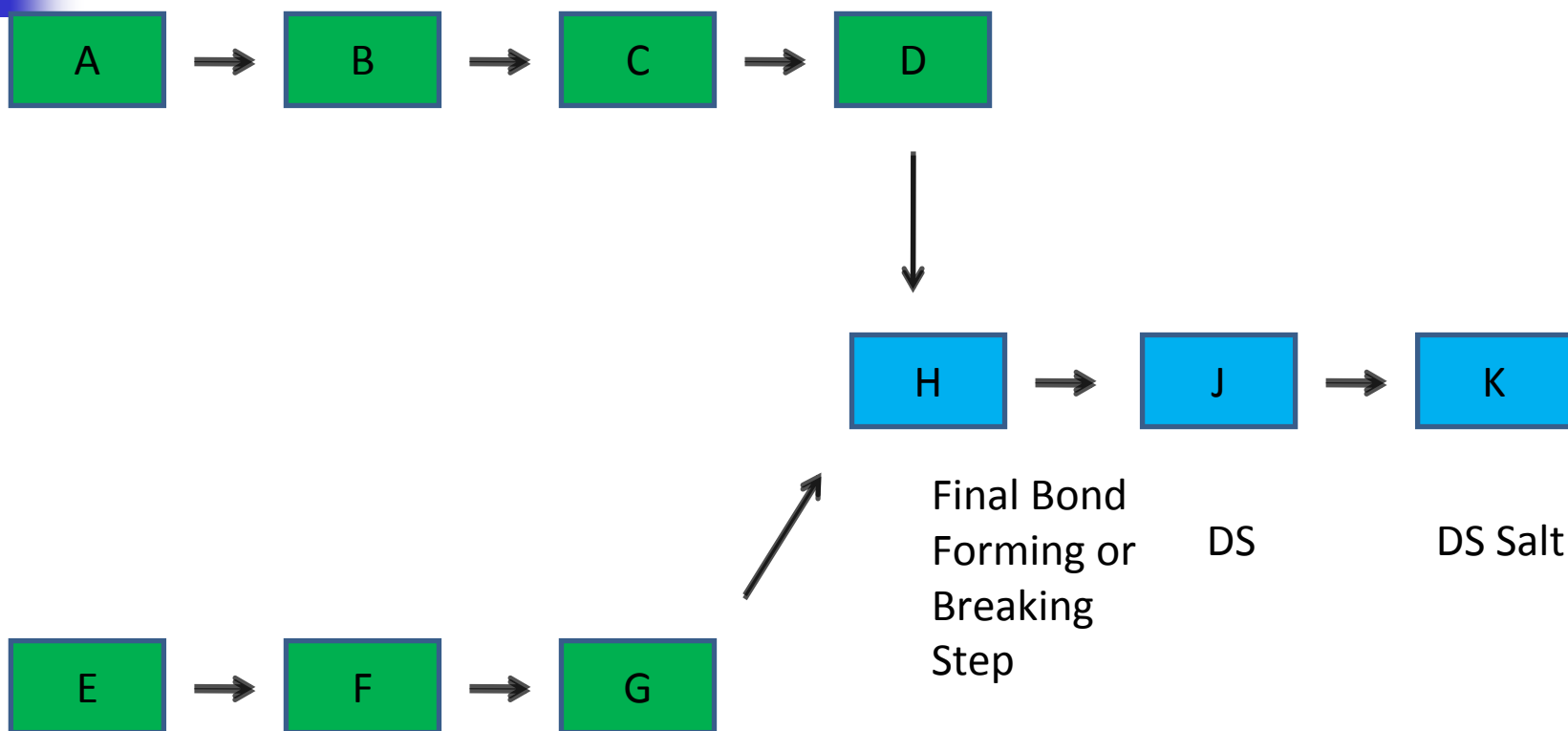
- Strategic Approaches
 - Retain Discovery Route
 - About 50% of the time
 - Generally with shorter, simpler syntheses
 - Generally requires significant process optimization
 - But this is done over time and not before first large scale lot is produced
 - Modify Discovery Route
 - About 25% of the time
 - Major changes to 1-3 steps
 - New Synthetic Route
 - About 25% of the time
 - Requires totally redesigned route even for very early development supplies
 - Particularly true for initially long syntheses



DS Synthesis Technology

- Preferred Synthesis Strategy
 - Convergent Synthesis
 - Final bond forming/breaking step defined
 - Final purification step defined
 - Knowing that it will not likely be final process
 - Affords the ability to:
 - have final common steps for drug substance
 - Changes to synthesis of penultimate intermediates reduces risk if final steps are the same
 - Define salt form early (when appropriate)

DS Synthesis Strategy



Synthesis Technology - Risk Investment Strategies



- What is trigger to:
 - Purchase raw materials?
 - Prepare key intermediate?
 - Commit FTEs?
 - Evaluate new synthesis technology or optimize existing technology?
- What strategy best balances money and people investments with attrition
 - Attrition before candidate nomination
 - Attrition after candidate nomination
 - Speed vs. milestone driven investments



Synthesis Technology - Risk Investment Strategies

- Decisions based on:
 - Priority for candidate
 - Risk tolerance for early investments
 - Competitive environment
 - Technology challenges

Synthesis Technology - Risk Investment Strategies



- Examples of Issues to Consider Prior to Making Resource Investments
 - Is analog program based on common intermediate?
 - If so, it makes sense to prepare larger quantity of intermediate early
 - With complex synthesis technology, development of improved technology early may make sense
 - If it speeds:
 - Analog synthesis
 - Evaluation of lead analog
 - Progression to nomination



Drug Substance Form

- Objectives For Drug Substance Form
 - Crystalline
 - Non-hygroscopic
 - Stable
 - Solid State (for storage)
 - target is >6 months initially
 - In DP
 - Bioavailable



Drug Substance Form

- Recommendation

- Identify Preferred Salt Form/Lowest Energy Polymorph EARLY When Appropriate
 - But does not have to be scorched earth effort at this stage
 - Depends on facts
- Can potentially impact all future work
 - Purity profile
 - Stability profile
 - Formulation Development
 - Analytical Method Development
 - And potentially bioavailability
- G. Quallich will discuss salt/polymorph selection strategy in detail



Drug Substance Form

- Particle Size
 - When does it need to be addressed?
 - Depends on issues
 - But certainly when compound has poor solubility and poor permeability (Category III and IV) targeted for oral delivery
- Can impact:
 - Bioavailability
 - Manufacturability of solid oral drug product
 - E. Fiese to address

Drug Substance Demand and Supply



- Material Supply
 - An Early Issue – Almost always
- Material Demand
 - In Discovery
 - Material demand ranges from milligrams to grams
 - For biological characterization, preliminary safety evaluation and pK analysis
 - Following Candidate Nomination
 - Material demand for further characterization, early animal safety studies, and development studies ranges from 20-300 g
 - Depends on potency and desired studies
 - For GLP, GMP, and DP Development Activities
 - Material demand ranges from 50g to 2 kilograms
 - There are always exceptions, but majority of drug candidates can be moved through safety studies and to Phase I using 1-1.5 Kg of material



Drug Substance Supply – NonGLP Material

- Material Supply
- Pre-Candidate Nomination
 - Strategy depends on:
 - potency of analog
 - complexity of synthesis
 - use of common intermediates
 - quantity required
- Post Nomination
 - Initial manufacturing focus
 - Material to support full characterization of nominated drug and support initial development activities
 - DP development, nonGLP safety studies, DS form
 - Prepare 20-300 g by any process if feasible



DS Supply – GLP and GMP Materials

- Material Supply Strategy
 - GLP Animal Safety Study Supply
 - GMP Clinical Supply
- Options
 - Single lot for both activities
 - Two different lots

DS Supply – GLP and GMP Material

- Single Lot
 - Covers material needs for DP development, GLP safety studies, and GMP clinical studies
 - Same purity profile assured for initial clinical studies since same lot of DS used in GLP safety studies (from DS perspective)
 - Single Lot Strategy
 - Most cost effective
 - but somewhat slower to GLP material supplies
- Two Lots
 - GLP Lot
 - Material suitable for use in GLP safety studies can be prepared in most any laboratory facility
 - Covers early DP development requirements and GLP safety studies
 - GMP Lot
 - Covers needs for initial clinical studies
 - Potential for different purity profile between lots, thus may require extra purification
 - Two Lot Strategy
 - More expensive, but faster to GLP supplies



DS Supply – GLP and GMP Material

- Single Lot Strategy vs. Two Lot Strategy
- Preference depends on:
 - Development strategy
 - Technical issues
 - Costs
 - Projected Timelines
 - But for smaller companies, time savings generally push decision in favor of two lot strategy



DS Sourcing

- Starting Material Suppliers
 - Ensure supply
 - Identify several potential suppliers
 - Qualify at lab scale
 - Can be coordinated with GMP Manufacturer
- GMP Manufacturer (if there are no internal facilities)
 - Define required capabilities
 - Types of reactions
 - Cytotoxic or non-cytotoxic requirements
 - Quality Systems and Analytical Capabilities
 - Ability to retain IP related to DS synthesis
 - Timing
 - Cost
 - Request for Proposal and lead time
 - 3 plus months to execute agreement (CDA, review of RFP, manufacturing agreement)
 - 6-9 months lead time for planning manufacturing
 - Based on loading at CMO



DS Purity

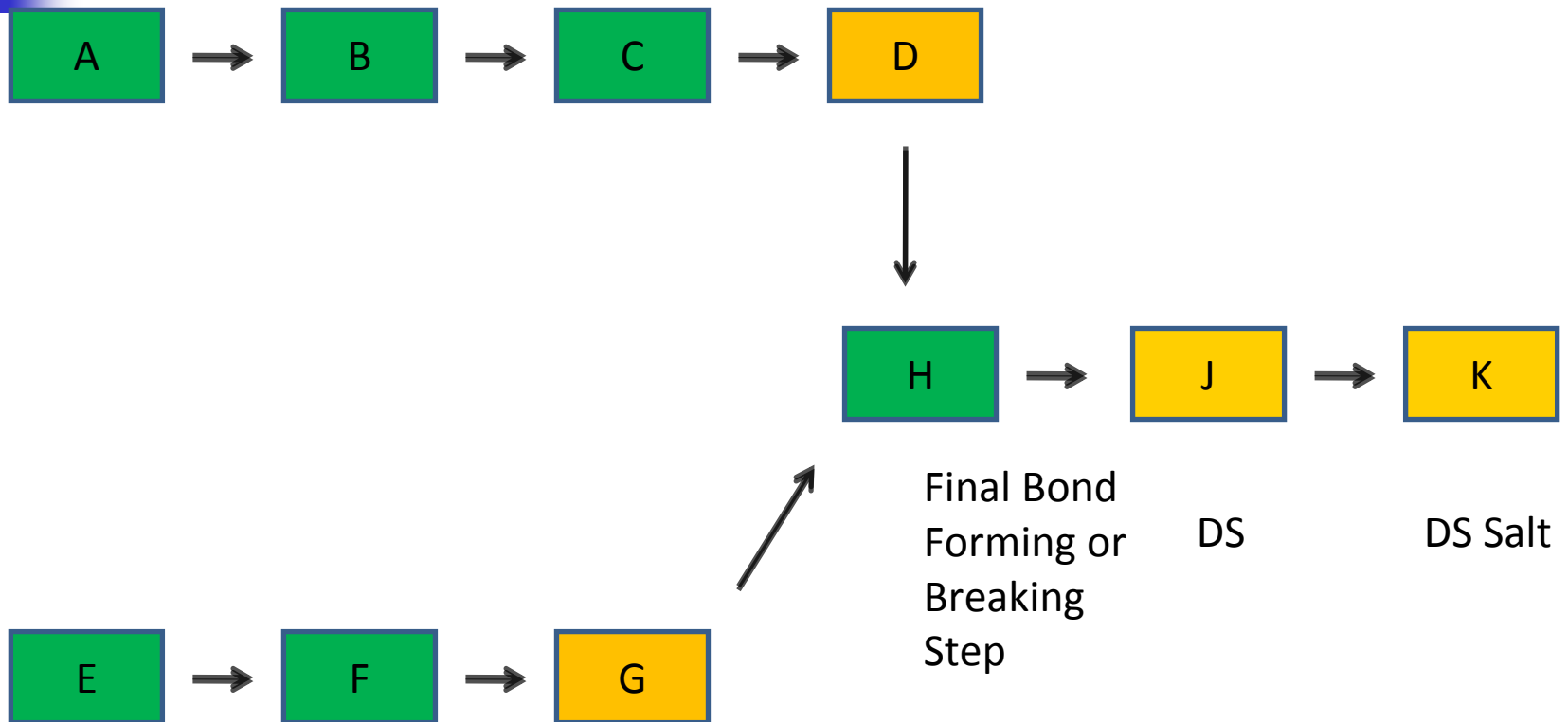
- DS Purity Covers Three Major Categories
 - Impurities
 - Qualified Impurities
 - Identified and Unidentified
 - Unqualified Impurities
 - Identified and Unidentified
 - Residual solvents and metal catalysts
 - Genotoxic Impurities



DS Purity

- What is impurity control strategy for initial lots of DS?
 - Target - $\geq 98\%$, no single impurity $> 0.5\%$
 - Goal: establish culture that quality does matter
 - But this is target and facts should be considered and goals adjusted as appropriate
 - What are purity control check points?
 - Key purity control points in synthesis are shown on next slide
 - Drug substance and its salt – J and K
 - Quality of precursors in convergent synthesis – D and G
 - Starting materials – to be discussed
 - For initial synthesis, no specifications will be in place, but collection of data begins here and helps build understanding for control of purity in future lots.

DS Purity Control Strategy





DS Specifications

- Basis for specifications
 - Established by the quality of material utilized in:
 - initial GLP animal safety studies
 - genetic toxicity studies
- Impurity Specifications Cover
 - Qualified Impurities
 - Identified and Unidentified
 - Unqualified Impurities
 - Identified and Unidentified
- Requires Appropriate Impurity Indicating Analytical Method



Specifications and ICH Guidelines

- Q3A (R2) Impurities in New Drug Substances (www.ICH.org)
 - ***APPLIES TO COMMERCIAL PRODUCTS***
 - Philosophy can be used for development candidates but actual levels should not be adopted
 - Specifications should cover:
 - Specified impurities
 - Both identified and unidentified
 - Unspecified impurities
 - Both identified and unidentified
 - And is set at the qualification threshold



Impurity Guidelines

- Unspecified Impurity Specification/Qualification Threshold
 - The level below which new impurities do not need to be qualified
 - ICH Limit for Commercial Products
 - $\leq 0.10\%$ for unidentified impurities
 - ≤ 0.14 for identified impurities
 - Options for Defining Unspecified Impurities Specification/Qualification Threshold for Development Candidates
 - 0.2% to 0.5%
 - All have been utilized for development candidates
 - Depends on company culture and experience
 - May be influenced by therapeutic area
 - For example oncology vs. metabolic disease



DS Specifications

- Setting Specifications for Impurities
 - Process capability – can not be utilized
 - There is no history, this is first or second lot of drug substance
 - Multiple Argument – can not be utilized
 - No human experience.

DS Specifications – Process Related Impurities

- An Example
 - Impurity A is present in DS lot used in animal safety study at 0.4%
 - Can be identified or unidentified
 - What is specification that should be set?
- Options
 - 1. Level plus unspecified impurity/qualification threshold (0.2%)
 - Specification would be set at 0.6%
 - 2. Level times fixed multiple (2X)
 - Specification would be set at 0.8%
- Both are utilized by various companies
 - Qualification Threshold – can range from 0.2% to 0.5%
 - Fixed multiple – can range from 1.5X to 3 X
 - With cap so specification can not exceed a given percent
 - ICH Guidelines
 - A few companies even use ICH guidelines for development candidates
 - Not recommended



DS Specifications

- Solvents

- Q3C(R3) – Impurities: guideline for Residual Solvents
- In general, residual solvent levels should be set at accepted levels based on ICH Guidelines for residual solvents

- Residual Catalysts

- EMEA Draft Guidance – January 2007
 - Guideline on the Specification Limits for Residues of Metal Catalysts – CPMP/SWP/QWP/4446/00
 - This has become guidance in absence of FDA and ICH guidelines
 - Flexibility is provided based on human dose and frequency of dosing



Genotoxic Impurities

- Key Safety and Regulatory Issue
 - Need to address the presence of actual and potential genotoxic impurities in drug substance
 - EMEA – Guidance Document
 - CPMP/SWP/5199/02 Guideline on the Limits of Genotoxic Impurities
 - PhRMA Position Paper
 - Regul. Toxicol. Pharmacol. 44 (2006) 198
 - Regulation of Genotoxic and Carcinogenic Impurities in Drug Substances and Drug Products, Trends in Analytical Chemistry, 25 (2006) 790.
- Genotoxic Impurity May Be:
 - Process Intermediates
 - Process Related Impurity
 - Reagent
 - Degradation product



Genotoxic Impurities

- FDA has put INDs on hold pending resolution of issues related to:
 - Known genotoxic impurities
 - Potential genotoxic impurities
 - Structural Alerts
- FDA is using in silico analyses to screen INDs for structural alerts
 - DEREK and possibly other systems



Genotoxic Impurities

- Genotoxic Impurities - Recommendation
 - Screen via in silico analysis for structural alerts for identified compounds or with high probability of being present
 - Process intermediates
 - Process related impurities
 - Reagents
 - Degradation products
 - If structural alert identified, develop strategy to address
 - Eliminate from process (i.e. change synthesis to avoid presence of intermediate)
 - Test in Ames study
 - If negative, treat as normal impurity
 - If positive control level
 - Justify by knowledge of activity of closely related compound
 - Drug substance for example
 - Control to avoid formation and verify
 - At intermediate stage
 - At final DS
 - To levels based on above documents



Genotoxic Impurities

- Strategic Approach
 - Preferred synthetic strategy:
 - Contains no genotoxic intermediates or reagents
 - Control Strategy
 - Preferred
 - Control at intermediate step – 1-3 steps from drug substance
 - Allows levels of genotoxic intermediate/impurity to be controlled prior to drug substance
 - i.e. no specification at drug substance
 - Alternative
 - Control with appropriate specification
 - Defined by stage in development etc.



Genotoxic Impurities

- Potential to Form During Synthesis or/on Stability
 - Strong acid addition salt crystallized from solvent containing an alcoholic solvent
- Example
 - Cpd 1 is isolated as a methanesulfonate salt from MeOH/Water
 - Potential to forms methyl methanesulfonate
 - Known mutagen
 - Need to avoid formation
 - Option 1 - Eliminate use of methanol
 - Option 2 – Demonstrate that methyl methanesulfonate is below guidance levels (EMA and PhRMA White Paper)
 - Recommendation
 - Do not use alcoholic solvents in final processing step with strong acid addition salt of drug candidate



Impurities

- Impurity Identification Strategy
 - For initial lots, impurities do NOT have to be identified if qualified by presence in animal safety material
 - Identification strategy
 - Start with largest impurity and work down
 - But all impurities greater than 0.1 or 0.2% do not need to be identified prior to start of phase I clinical studies



Regulatory Strategy

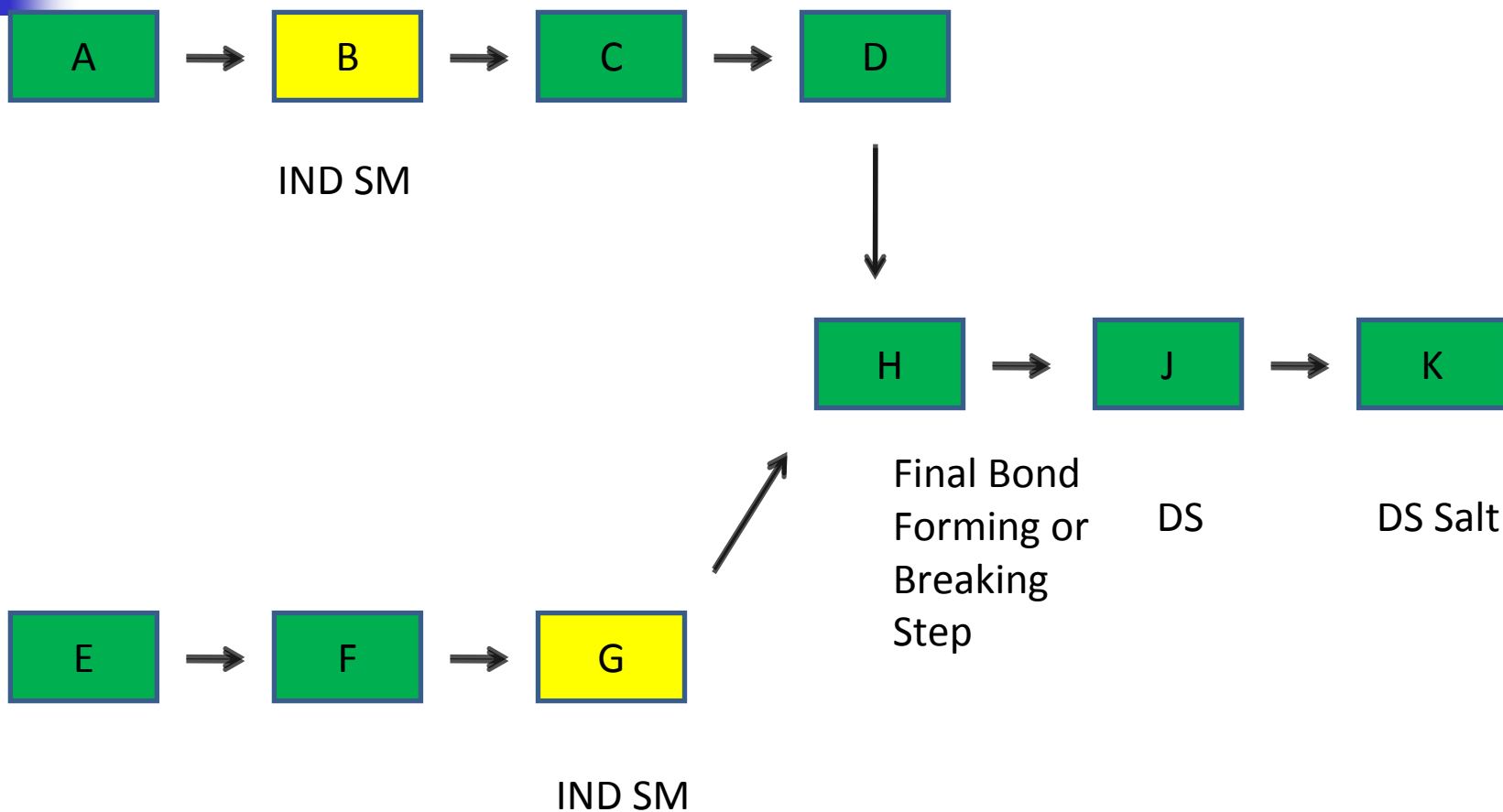
- PreIND Meeting
 - Separate CMC meeting/discussion from toxicology and clinical meeting/discussion
 - Raise specific questions related to CMC development strategy for which feedback is desired
 - Examples
 - Genotoxic impurity strategy
 - Any key specification questions
 - Stability plan
 - Can be actual meeting or feedback from FDA based on information provided



Regulatory Filing Strategy

- Synthesis
 - All steps do not need to be included in IND filing
 - Evaluate process
 - designate IND starting materials
 - GMP processing from IND SM
 - Control strategy for other steps

Synthesis Strategy





Success

- Initiation of Phase I clinical studies
 - But.....
 - What about ability to manufacture 10-50 kg?
 - What about economics?
 - Proprietary Position
 - Freedom to Operate
 - Patentable Matter



Cost of Goods Projects

- Early Stage Economic Analysis
 - Key question:
 - Are Cost of Goods (COG) a Concern?
 - Yes, No, Maybe
 - Quick assessment may be feasible with key assumptions:
 - Cost of Goods
 - Projected Cost of DS and DP
 - Projected Targeted Selling Price
 - Projected human dose
 - Royalty Burden
 - Answer Drives Resource Allocations



Cost of Goods Analysis

- Answer
 - COG No Issue
 - Then product could be
 - Low dose
 - Short synthesis
 - High Selling Price
 - No Royalty
 - COG Significant Issue
 - Major technical challenge
 - High dose
 - Low selling price
 - Significant royalty burden
 - Translates to:
 - Earlier commitment to optimization of synthesis



Intellectual Property Position

- Freedom to Operate
 - Is it known if process being operated is non-infringing?
- Patentable Matter
 - What is value?
 - Is it better to put in public domain?
 - Does it offer any real protection?
- May Impact Sourcing Strategy



Summary

- Candidate Nomination to Phase I
 - Requires integration of activities before and after nomination
 - With numerous partners
 - Speed important but:
 - Speed without management of risks will almost always take longer
 - Address quality issues (genotoxic impurities, metal residues, impurities) proactively