# Chemistry, Manufacturing, and Controls: How does a molecule become a physical medicine to be given to a human

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ASM/ESCMID

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# Presenters and Our Conflicts

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# Today's Session

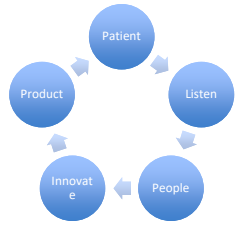
- We are presenting as though our company – and that's all of us in this room – has just in-licensed a new drug, X-1
- Our presentation is the last section of the "kick-off" meeting, during which the development team – and that's all of us in this room – describes the work necessary to advance X-1 to the next stage. Today, we are getting ready for Phase 3 clinical trials, and will share the CMC plans that are necessary at this stage
- Importantly, the company that discovered X-1 was very small and cash-limited. Accordingly, some activities that a larger company might do early in development were left to later. To us, everyone in this room

# Some Common Acronyms

- API: active pharmaceutical ingredient, i.e., the therapeutic molecule
- DP: drug product. The drug as presented to the pharmacy (e.g., tablets in a bottle; powder in a vial)
- GMP: Good Manufacturing Practices, i.e., the rules for manufacturing pharmaceuticals
- RSMs or SMs: Starting materials for manufacturing – at this stage, GMP are followed
- QA: Quality Assurance
- IND: Investigational New Drug, and application made to the FDA that supports clinical trials
- NDA: New Drug Application, wherein we include all data on a drug for review by the FDA

# X-1 Development Team Kick-off Agenda

- X-1 Introduction – what is it?
  - History at Company X
  - Target Product Profile
  - Microbiology
  - Clinical data to date
- Practical Matters
  - Project Code
  - Time Billing
  - Budget
- Initial Deliverables
  - Development Plan
    - Tox
    - Clinical
    - CMC
  - Timelines



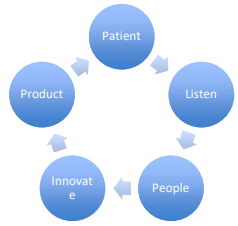
# Clinical Studies

| Study | Number subjects/patients (dosing) | Dosing | Status |
|---|---|---|---|
| Ph1 SAD/MAD | 60 | 5 mg to 400 mg single dose; 25 mg to 300 mg TID x 14d | Complete |
| Ph1 BAL/ELF | 52 | 100 mg single | Complete |
| Ph1 Renal impairment | 18 | 100 mg single | Complete |
| Ph1 Hepatic impairment | 18 | 100 mg single | Complete |
| Ph2 cystic fibrosis | 10 | 100 mg TID x 14 d | Complete |
| Ph1 Thorough QT | 50 | 300 mg single | Planning |
| Ph1 DDI | 36 | 150 mg x 2 | Planning |
| Ph3 VAP | 580 | 150 mg TID x 14d | Planning |
| Ph3 multi-site of inf | 200 | 150 mg TID x 14d | Planning |

# Ph3 Pivotal Trials

| | 1: Ph3 VAP | 2: Ph3 Multi-site of Infection |
|---|---|---|
| # patients on X-1 | 290 | 120 |
| # controls | 290 | 60 |
| Dosing | 150 mg TID x 14 d | 150 mg TID x 14 d |
| # sites | 200 | 50 |
| Enrollment rate | 0.1 pt/site/mo | ?? |
| Start | 3Q18 | 3Q18 |
| Complete | 2Q20 | 3Q21 |

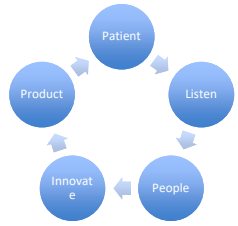
Note: both studies will utilized currently unapproved bedside diagnostic to screen for *Pa*; Study 2 may enroll patients who previously failed other tx and who have confirmed *Pa*



# Clinical Trial Drug Requirements

| Study | # pts | Doses/day | Days of tx | Total vials | +30% |
|---|---|---|---|---|---|
| Ph3 VAP | 290 | 3 | 14 | 12,180 | 15,834 |
| Ph3 Multi-site | 120 | 3 | 14 | 5,040 | 6,552 |

Total vial requirement for Ph3 is 22,386 vials. Each vial contains **150 mg**; estimated API need is **approx 3.4 kg**



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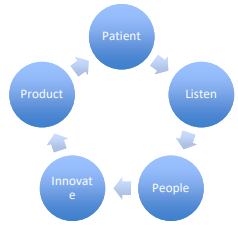


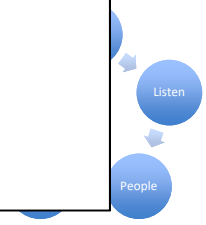
# X-1 Batch History / Inventory

| | Lot # | Quantity | GMP? | Use | Remaining Inv |
|---|---|---|---|---|---|
| API | 12345 | 50 g | No | Early pharmacology | <2 g |
| API | 23456 | 250 g | No | GMP tox + stability | 20 g |
| API | 34567 | 2 kg | Yes | Ph1/2 + stability | 300 g |
| DP | X_1_123 | 100 mg; lot size 1000 vials | Yes | Ph1 + stability | 10 vials returned from clin |
| DP | X_1_234 | 100 mg; lot size 1000 vials | Yes | Ph1/2 + stability | 300 vials |

These are the lots that the company from which we in-licensed X-1 had made at contract manufacturers.

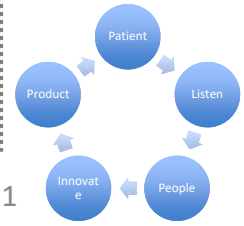
Current price for X-1 API is **$1,000/gram** from an unoptimized process, on esoteric equipment, limited options for large scale manufacturing.

Current drug product vials are X-1 (no excipients) lyophilized in a vial; cake is inelegant. Current stability suggests **15 months expiry at refrigerated**.



# Technical Stage-Gate Deliverables Template

| | Research | | Development | | | | Commercial |
|---|---|---|---|---|---|---|---|
| | Pre-Candidate Nomination | IND Enabling | Phase I Dev | Phase II Dev | Phase III Dev | Reg Submission | Post Approval |
| Technical Deliverables | ▪ API Form<br>▪ Discovery Knowledge Transfer<br>▪ API for IND Enabling Studies<br>▪ Non-Clinical Form-ulation | ▪ Phase 1 CTM<br>▪ CMC section of IND<br>▪ CMC Development Plan to POC<br>▪ Pre-IND meeting w/ FDA | ▪ Phase II CTM<br>▪ Preliminary COG Assessment<br>▪ Initial Safety Assessment<br>▪ Scalable API Processes | ▪ Phase III CTM<br>▪ Commercial CMO & CapEx<br>▪ API Route Process Lock<br>▪ DP Formulation Process Lock<br>▪ CMC Development Plan to Launch<br>▪ Starting Materials<br>▪ Manufacturing Costs<br>▪ Market Image Definition<br>▪ Proposal for 2nd Generation<br>▪ Occupational Health Assessment | ▪ Tech Transfer package for API and DP<br>▪ End of Phase II meeting w/ FDA<br>▪ Registratio n Batches on Stability<br>▪ Genotox Assessment<br>▪ NDA Specifi-cations<br>▪ Launch Strategy | ▪ CMC section of NDA<br>▪ PAI Readiness<br>▪ Validation Readiness<br>▪ Launch Readiness Plan<br>▪ Shipping Study Report<br>▪ Launch and Safety Stock<br>▪ Updated Expiry | ▪ Post Approval Commit-ments<br>▪ Next Generation Process |



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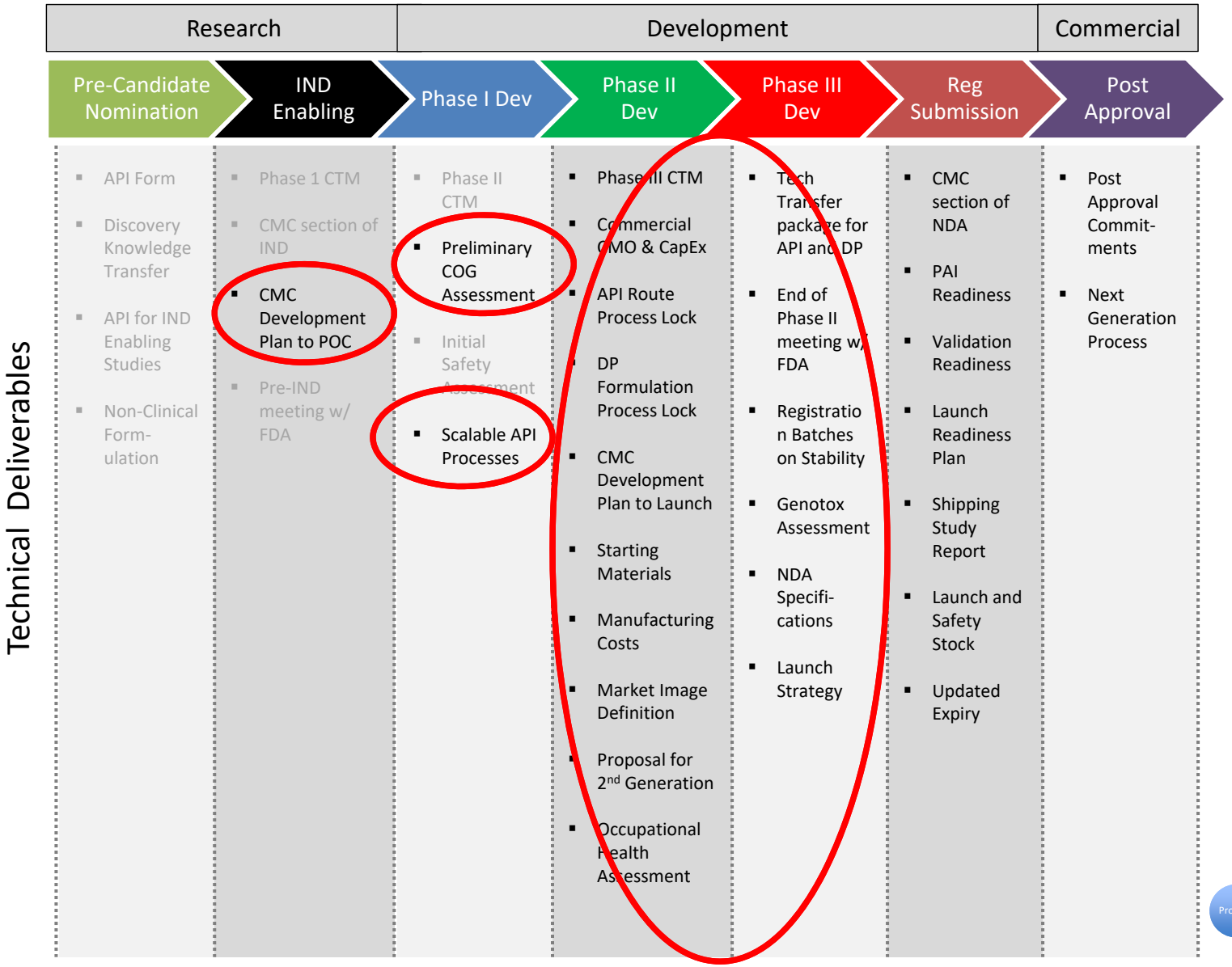
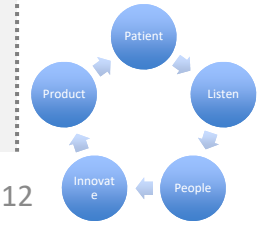
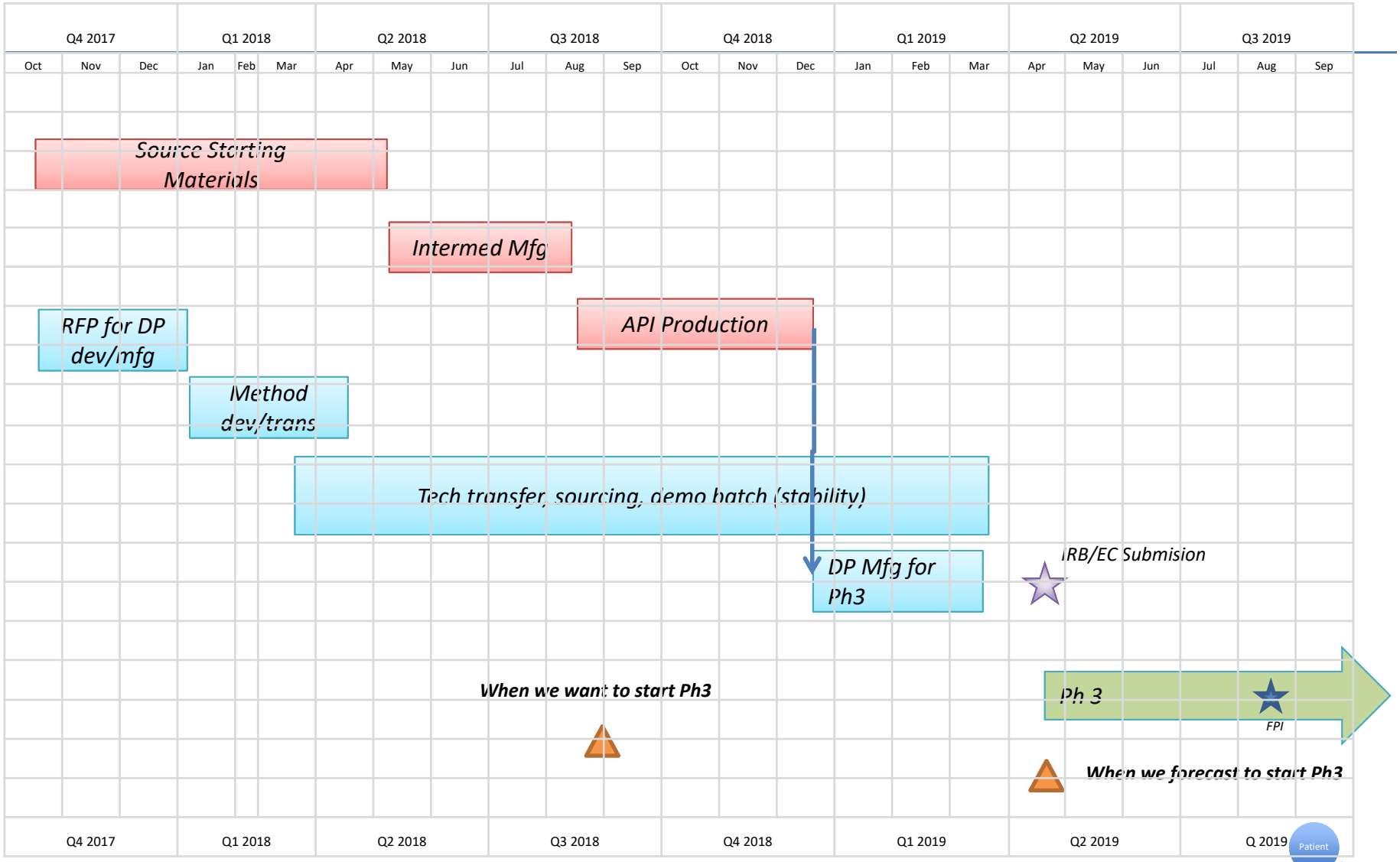
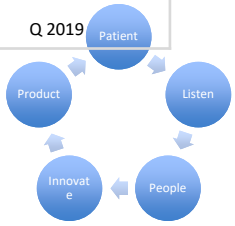


# Integrated Timeline – Ph3 Supply



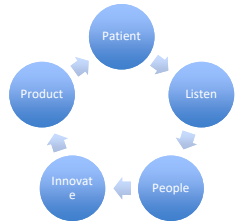



## Slide 13

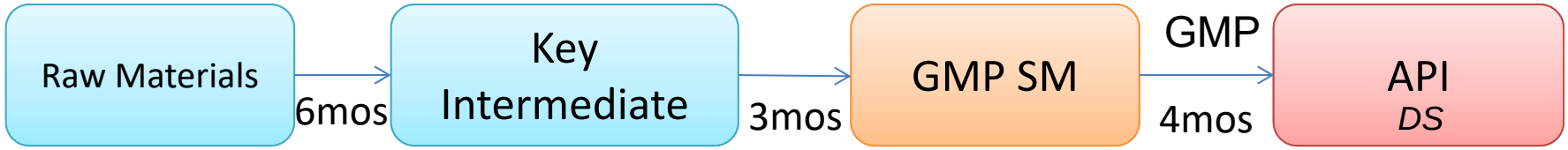
**EH1** Evan Hecker, 9/4/2017

# API Considerations

*Evan Hecker*



# 1st GMP API Process – Clinical supply achieved!

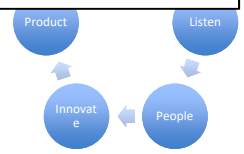



CMO: Commodity CMO | Chinese CMO | US Based API Supplier

Issues: COST | Scalability | Capability | Robustness

Clinical trial supply achieved, WE ARE IN THE CLINIC

- Fit for purpose process used in Phase 1
- Medicinal chemistry lab route slightly improved and scaled for early clinical deliveries
- Drug substance produced as single crystalline polymorph



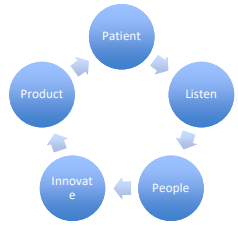
# API Considerations – Aligning Priorities

*The best plans will align and overlap development activities to maximize efficiencies of effort, time, and capital. CMC is often on critical path these days…*

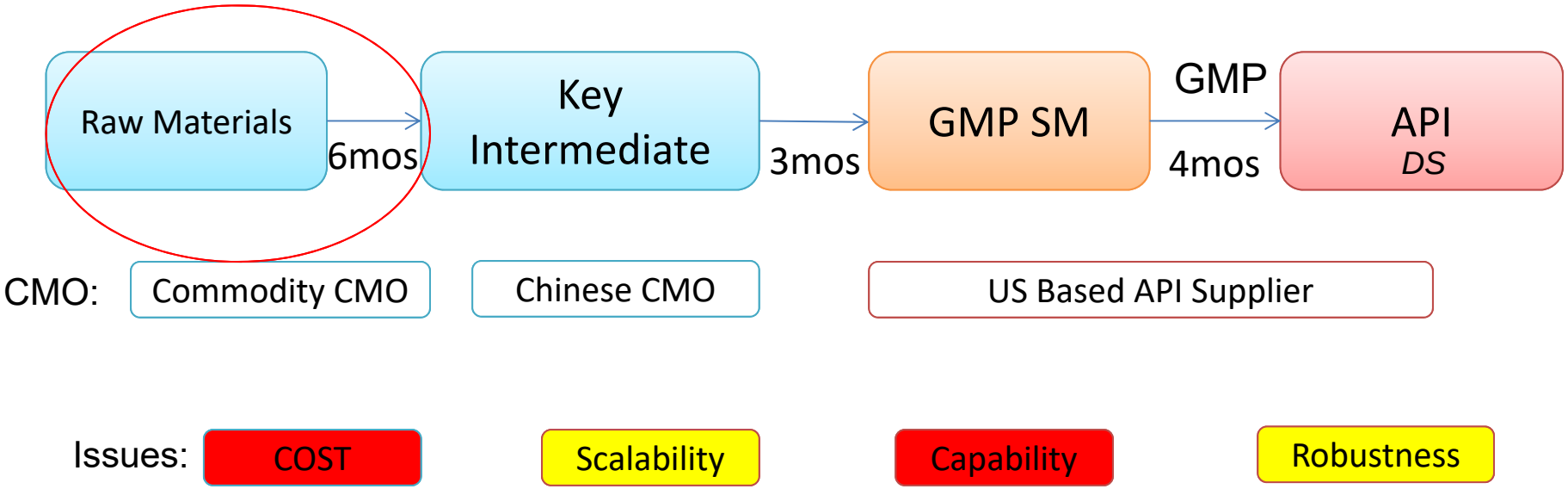
- Priority #1 – Supply the Clinic

- Priority #2 – Support clinical development
  - Priority #2a – Generate data to support clinical supplies and studies ongoing
  - Priority #2b – Support all analytical, formulation, EHS, and tox activities supporting NDA

- Priority #3 – Plan for commercial

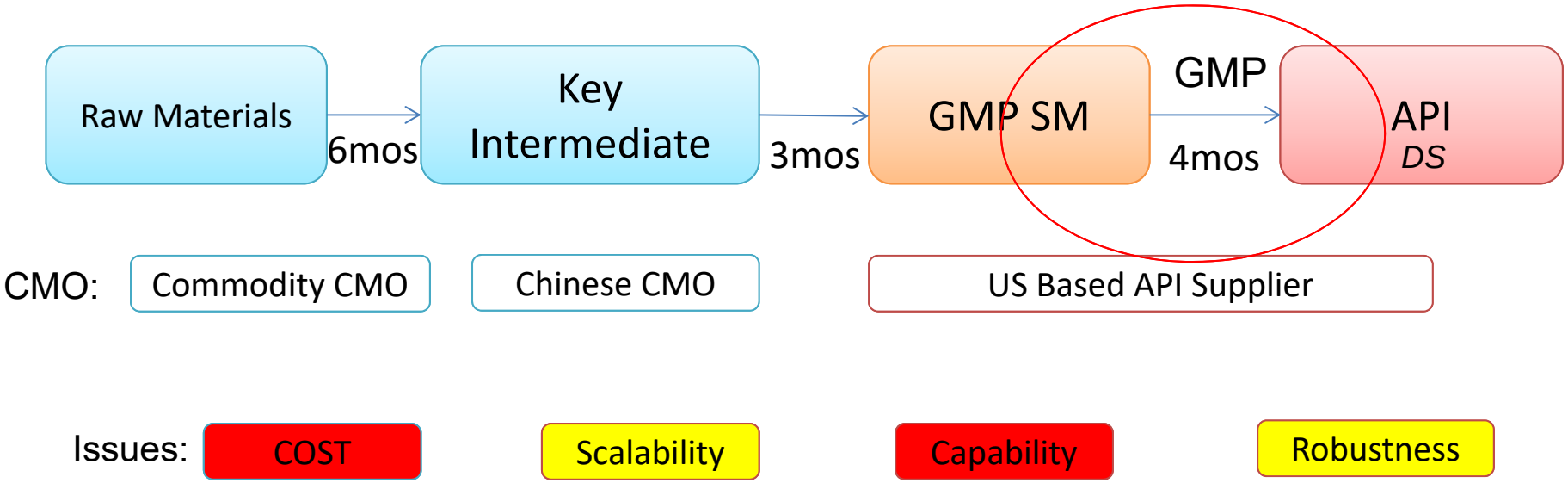


# API Priority #1 – Supply the clinic




- API is longest lead time. From commodity raw materials ordered to DS release will be at least <u>1 yr.</u>
  - Mitigation = stage GMP building blocks at risk to save 6mos

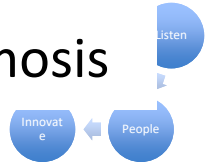
# API Priority #1 – Supply the clinic




- Rule of thumb = 1month/GMP step
  - Mitigation = for early clinic, only perform 2-3 GMP steps. This is not acceptable for commercial.
  - Phase 3 and beyond: will need to agree to GMP SM with regulatory authorities – likely earlier in synthesis

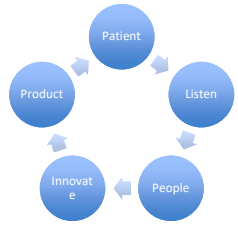
# API Priority #1 – Supply the clinic

- CTM is estimated to require ~4kg active. Target 2x to mitigate DP batch failures and support stability and processing losses.
  - Consideration: one batch to supply all DP at start vs two+ batches throughout study?
  - Consideration: API process is currently expensive (~$1,000/g). 8 kg for clinical supply will be **$8 M.**
    - Can we afford this? Can we afford not to?
    - What improvements can we make to the process without impacting our timeline?
    - Invest $ early to avoid esoteric equipment, i.e. HPLC purification, ion exchange chromatography, reverse osmosis



# API Priority #2 – Support Clinical Devt

- Priority #2a – Generate data to support clinical supplies and studies ongoing
  - Stability data, impurity tracking
    - API and intermediate stability:  assume additional material is synthesized to support these activities
    - Stability performed under ICH conditions
    - Impurities - need to establish specifications and work with toxicology to define what has been qualified to date
    - New impurities may trigger new tox
  - GTI assessment, EOP2 package, batch history
    - Work closely with tox to map potential GTIs in the process; are they eliminated?
    - EOP2 will be opportunity to review control strategy with FDA, discuss scale-up and validation, propose GMP SMs.



# API Priority #2 – Support Clinical Devt

- Priority #2b – Support all analytical, formulation, EHS, and tox activities supporting NDA
  - API for these activities may not need to be GMP. For example, align API development work to validate analytical methods, qualify new process impurities, and evaluate environmental tox with demo batches or tech transfer engineering batch.
  - Environmental tox will require large quantity of API (up to 500 g)