Revising CFR 314.70

FDA Public Meeting

February 7, 2007

Rockville MD

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SST SST Corporation

SST Business Model

- Represent numerous API & Intermediate Manufacturers worldwide.
- Market and Sell APIs & Intermediates to both the Brand and Generic Industries in the US.
- Provides a unique Regulatory vantage-point.

SST Regulatory Model

Type II DMF Holder

(A)NDA Sponsor

API Manufacturers/Suppliers

Customers

Industry Regulatory Model

Type II DMF Holder  (A)NDA Sponsor

- Historical Model for Generic Industry
- Widespread model (40%) for the Brand Industry due to Outsourcing

SST's Business Interest

- Maintain Supplier competitiveness.
- Introduce new synthetic methods, equipment, alternate sites, specifications, PAT techniques.
- Encourage Change / Innovation.
- Same goal as Agency's Quality Initiative.

Presentation Perspective

- Drug Substance & DMF Holder

rather than

- Drug Product & (A)NDA Sponsor

Presentation Topics

- Five Points to Consider in the revision
- Relevance of the Risk-Based Paradigm
- “Outside the Box” Ideas

Point # 1

Revise Changes Guidance prior to CFR 314.70 Revision

Point # 2

Separate Drug Substance from Drug Product

Separate Sections

- Requires authors to adopt a presently absent Drug Substance mindset.
  - Filing recommendations for scale and equipment changes for small molecule APIs would be present.
  - Change from Centrifugation to Filtration would not be a PAS.*

*Particle Design of APIs Through Crystallization, W.Beckmann, Schering AG, American Pharmaceutical Review, Vol 9, Issue 6, pg 110 & ff, Sept. '06

Point # 3

Include DMF Holders

DMF Holders

- Filing mechanism format: Sponsor/DMF Holder
  - PAS/AM, CBE-0/AM, AR/AM.
- Expand the use of DMF Annual Update
  - Minor Changes via AR/AU.
  - No additional documentation to FDA.

Point # 4

Recognize the Final Step Continuum

Present Guidance

All Process Changes after the
Final Intermediate (FI)
require a
Pre-Approval Supplement !!

Final Step: Changes Guidance

Final Step: Science-Based

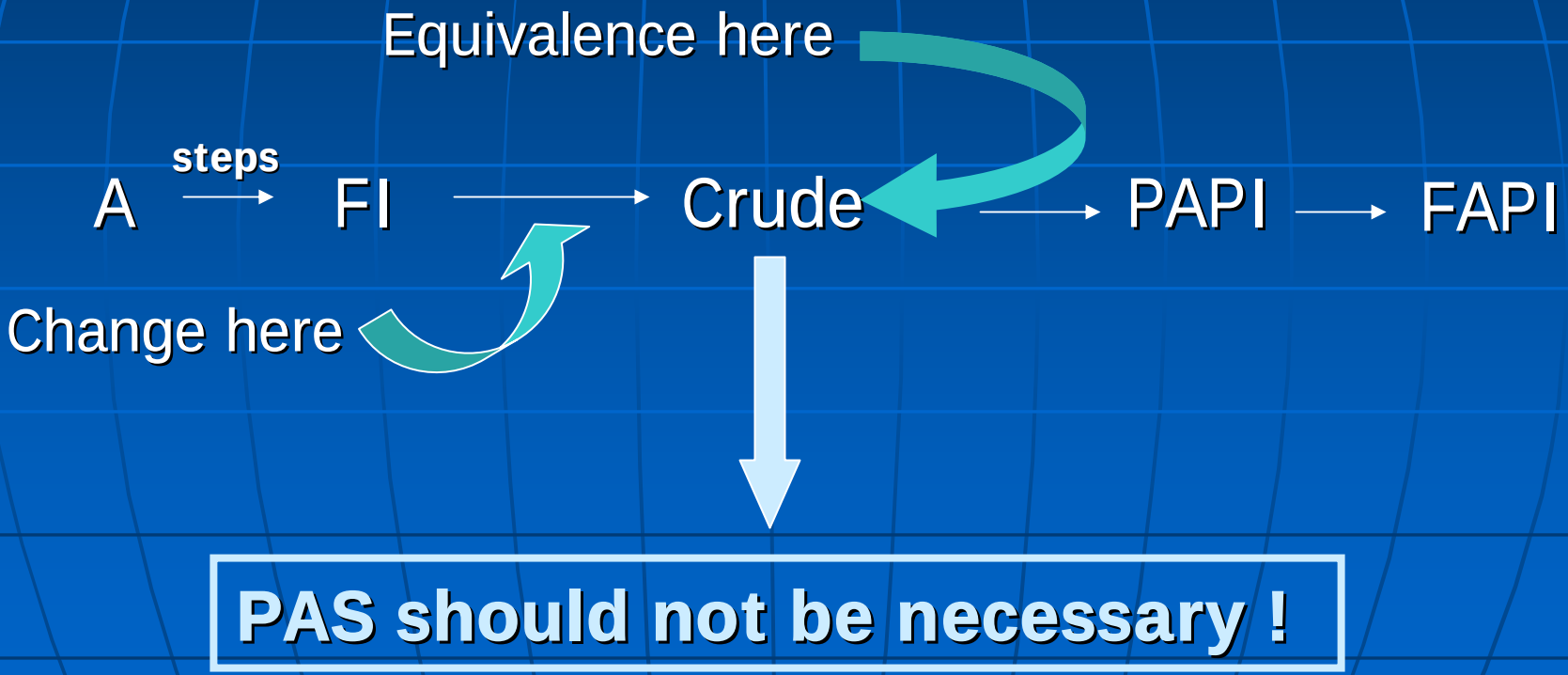
CAPI: Crude API

PAPI: Purified API

FAPI: Final API

*** Drying, Milling, Micronization, Blending, Packaging**

Final Step: Science-Based

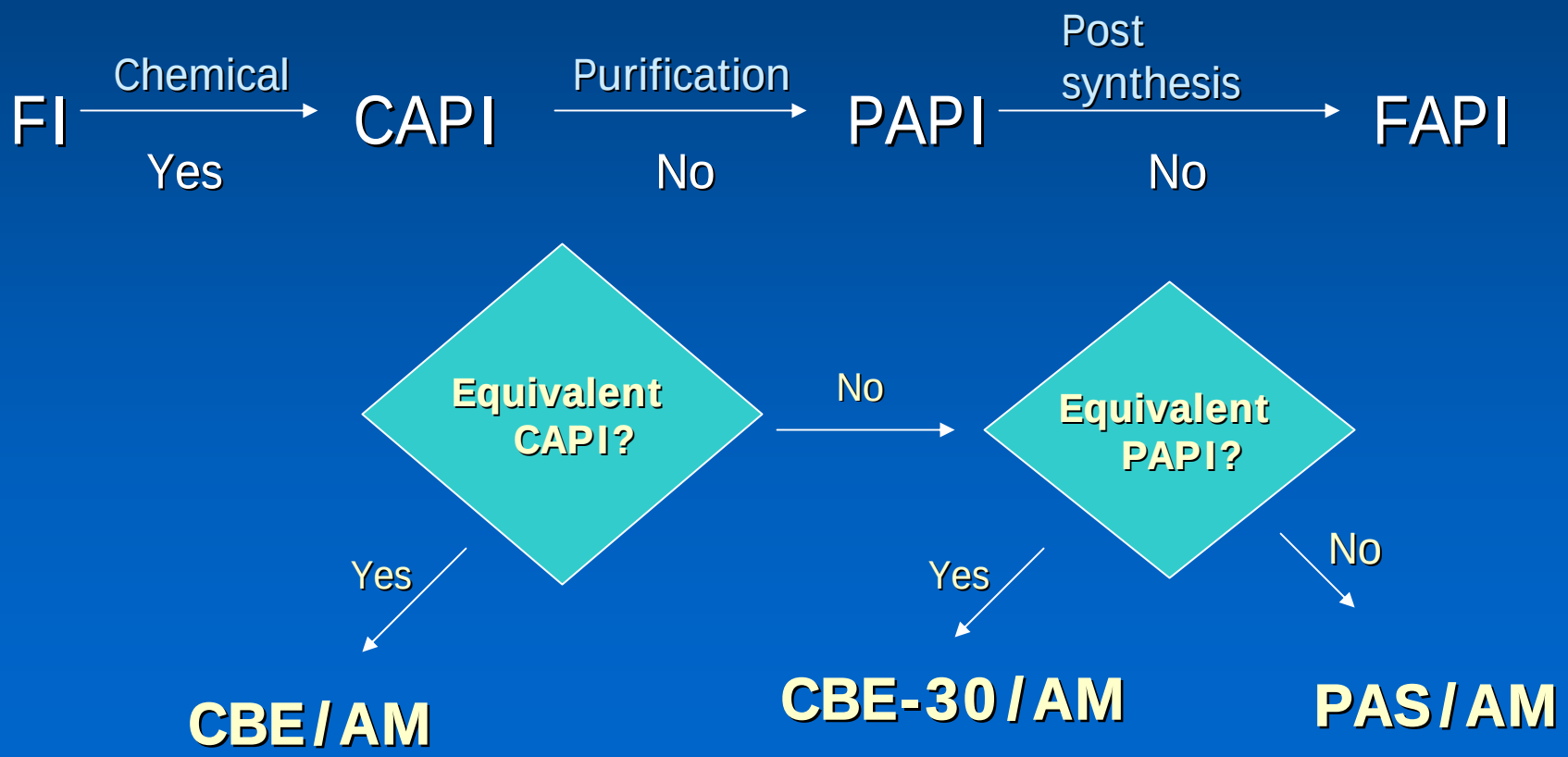


Phased Approach

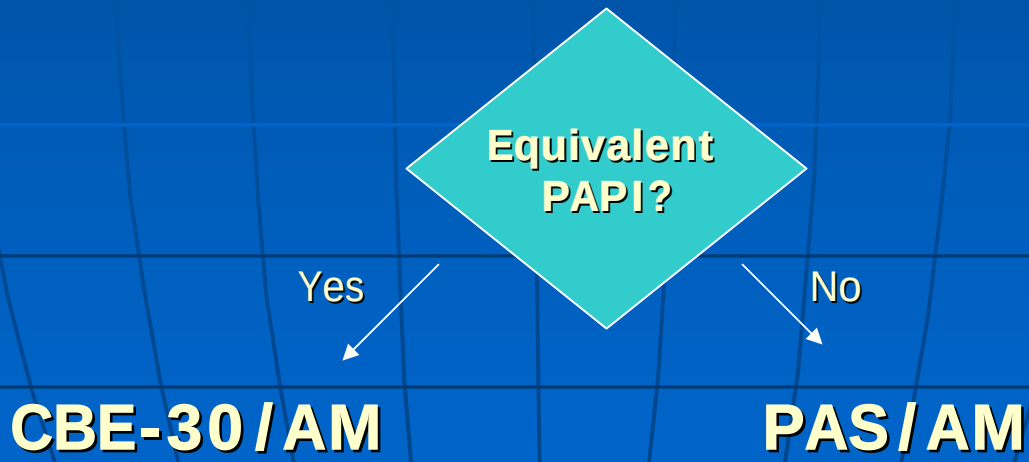
FI —Chemical→ CAPI —Purification→ PAPI —Post synthetic Operations→ FAPI

Yes	No	No
Yes	No	Yes
No	Yes	No
No	Yes	Yes
No	No	Yes
Yes	Yes	No
Yes	Yes	Yes
No	No	No, ie different FI

Chemical Phase Only

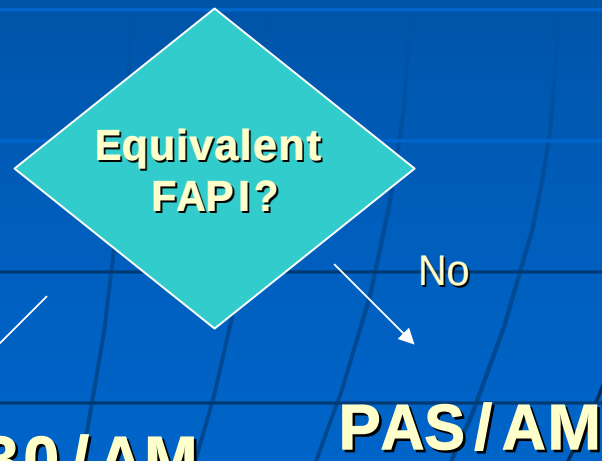


Purification Phase Only



Post Synthesis Phase Only

FI —Chemical (No)→ CAPI —Purification (No)→ PAPI —Post synthesis (Yes)→ FAPI



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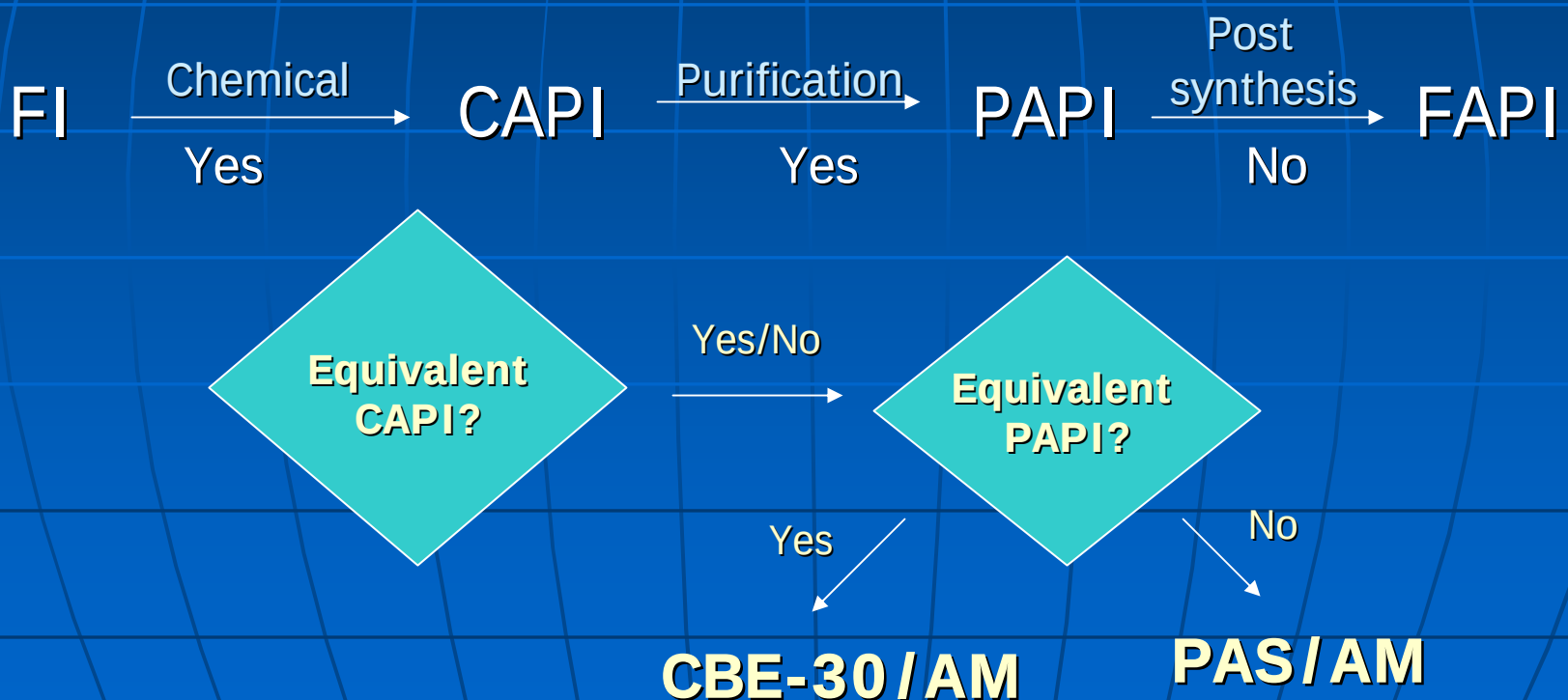
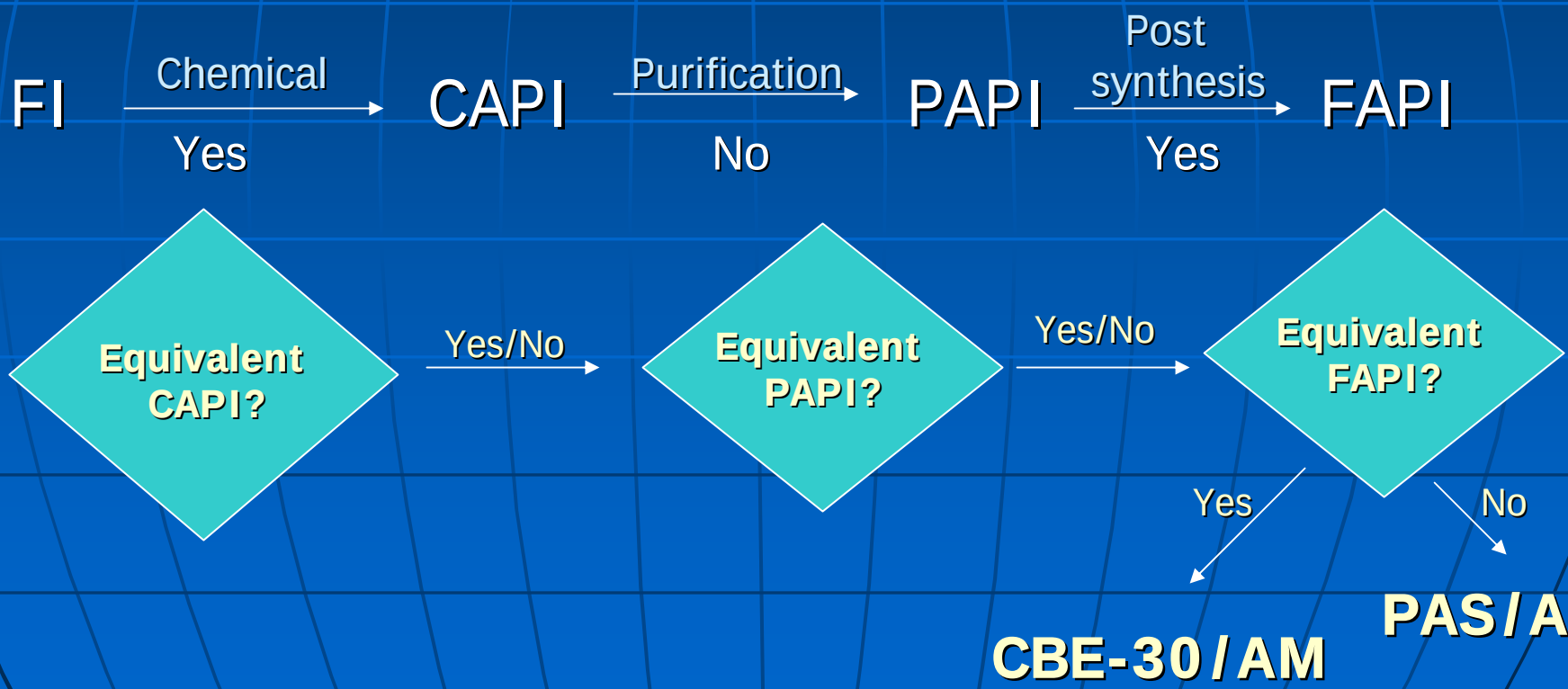
Chemical & Purification Phases



Chemical & Post synthesis Phases



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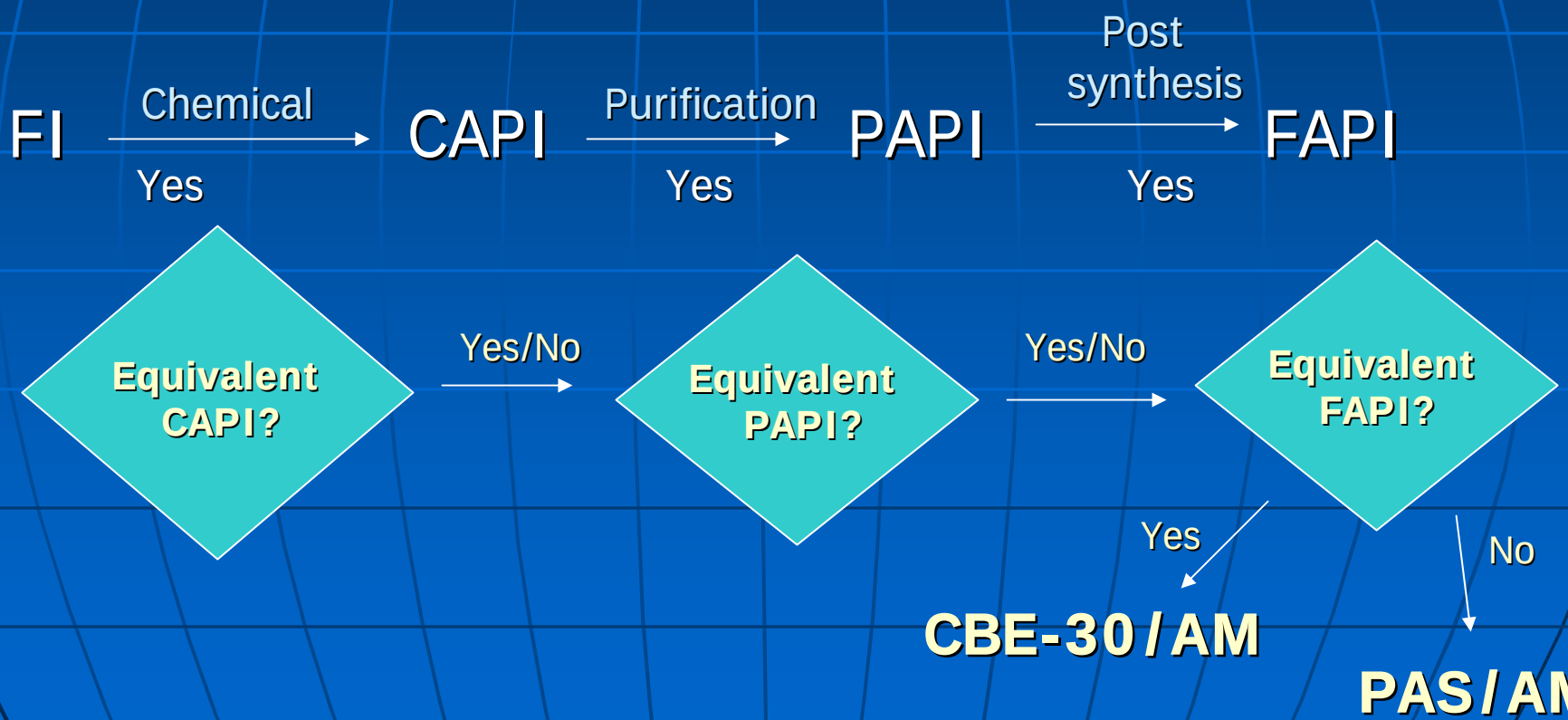
Change in all Three Phases



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Point # 5

Major Change Redefinition

Proposed Redefinition

- Major Process Changes
  - Must impact the API, not an upstream Intermediate
  - Proof of Equivalence needs supporting data beyond a specification comparison.
- This definition amenable to Scale and Equipment Changes, but other factors need consideration.
- Site and Specification Changes need a different analysis.

Relevance of the Risk-Based Paradigm ?

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Risk-Based Paradigm

- FDA only pre-approves Changes affecting the API and requiring more complex equivalence data, ie, Major.
- Totally analogous to the Risk-Based Inspection Model.
- Does not offer select companies reduction of filing mechanism; not needed.

Science - Based Paradigm !

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Outside the Box Ideas

- CBE 60/90 as Bridge to reducing PAS.

- High Quality CMC Information, not high volume.

- Special DMF Amendment for Changes; no link to (A)NDA Sponsor filing.

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To Summarize...

Thank You for your Attention!

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