

USP Pending Monograph Submission

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USP Pending Monograph

Objective

- New approach adopted by USP
- Enables monograph development and publication before FDA approval to a generic manufacture
- Under this approach, sponsors can work with USP to create a 'Pending Monograph' as authorized text
- Ultimate purpose is to have an official USP monograph ready as soon as possible after FDA approval of an application (i.e., ANDA)
- Resulting in an official USP monograph in a shorter time frame

USP Pending Monographs web site

www.usp.org/standards/pending/



Advantages

- The current guideline no longer requires publication in PF
- Pending Monograph request shall be accepted from a sponsor awaiting FDA approval even if there is an official monograph
- The pending and the official monographs will be merged resulting in a flexible monograph



Requirements

- Sponsor who have filed or intend to file with FDA an ANDA or DMF
- Should provide documentation of its intend to file an ANDA within 6 Months
- Documentation of DMF can be confirmed by providing a copy of DMF filing letter
- If the proposed monograph includes the use of new reference standard, same should be provided
- Include a request for confidentiality for a specified time



Requirements

- Prompt information to USP of any changes or modification or addition as a result of regulatory review and approval process
- Ensure consistency between the Pending monograph and product specific specification approved by FDA
- Information to USP if sponsor withdraws the application



Documents Required From Sponsor

- Chemical Properties
- Physical Properties
- Reference standards
- Name and lot number of any USP reference standard used
- List of proposed tests, procedures and acceptance criteria
- Complete chromatographic procedures including brand names of columns
- Representative chromatograms
- Validation data / reports
- Validation or verification data for general chapter tests



Documents Required From Sponsor

Certificates of Analysis

- For at least two Scale up batches / Exhibit batches
- If COA's are not available, data can be submitted in a summary table or other convenient format
- COA's as per submitted monograph



Documents Required From Sponsor

Packaging and Storage

- Packaging and Storage recommendations
- Any special handling instructions
- ANDA Sponsor : Include a copy of the approved package insert

Labeling information

- Labeling requirements regarding safety and handling of product



API Monograph Sponsor

Chemical information :

- ✓ Chemical name
- ✓ Structure
- ✓ Molecular formula
- ✓ Molecular weight
- ✓ Characterization data
- ✓ Polymorph data (if required)
- ✓ Representative spectra, e.g. IR, UV, etc.



API Monograph Sponsor

- Description
- Solubility
- Chiral purity : Limit of undesired isomer
- Residual solvents : Limits as per ICH guidelines or as per data
- Salt identification : Qualitative and / or quantitative method
- General test : Heavy metals, Sulphated ash, SOR, Water / LOD, etc



API Monograph Sponsor

- Assay
 - ✓ Titrimetric or HPLC method
 - ✓ Stability indicating method
- Chromatographic purity or Related substances
 - ✓ Intermediates / Impurity generation during synthesis
 - ✓ Degradation / Process impurities
 - ✓ Response factor of impurities
 - ✓ Impurity limits as per ICH guidelines or based on data



Drug Product Monograph Sponsor

- USP grade API
- 2-3 API source evaluation
- Different impurity profiling due to different synthesis process
- All pharmacopoeia impurities must elute in the method apart from in-house impurities
- Equivalency with USP methods to be shown incase methods used are non-pharmacopoeial
- Excipients : Preferably compendial grade



Method Development

- Literature search
- Extension of API method to drug product
- Extraction studies
- Stability indicating method
- HPLC columns : Method equivalency with different manufacturers
- In case drug substance or drug product is pharmacopoeia : method suitability / equivalency



Method Development

- Placebo interference with main peak and impurities is checked
- Forced degradation studies
- Impurity profiling
- Response factors of impurities
- Identification of process and degradation impurities



Dissolution Method Development

- Saturated solubility studies
- Official media information from SBA or 'Office of generic drugs'
- If placebo interference more than 2% by UV, HPLC method preferred
- Placebo interference with main peak is checked
- Dissolution % release till shelf life
- Analysis of innovator samples



Method Validation

- Specificity
Ability to assess unequivocally the analyte in the presence of components, e.g., impurities, matrix, etc.
- Forced degradation
Sample is subjected to various conditions to draw meaningful data
Acid / Alkali / Oxidative / Humidity / Thermal / Photolytic
- Precision
System precision, Method precision, Ruggedness
- System suitability
Equipment, analytical procedure, column,



Method Validation

Accuracy

Expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and value found

- Dissolution

Acceptance criteria : % recovery is in the range 95 – 105

- Assay

Acceptance criteria : % recovery is in the range 98 – 102

- Related substances

Acceptance criteria : % recovery is in the range 80 – 120



Method Validation

- Linearity
 - ✓ Response factor for impurities
 - ✓ Linearity of main analyte
- Limit of Detection and Quantitation
 - ✓ S/N of 3 : 1 and 10 : 1 for establishing LOD and LOQ
 - ✓ % RSD of 10 and 33 for establishing LOD and LOQ
- Stability of analytical solutions
 - ✓ Standard and sample solution stability



Method Validation

- Robustness
 - ✓ Variation due to change in mobile phase composition
 - ✓ Variation due to change in pH of mobile phase
 - ✓ Variation due to change in flow rate
 - ✓ Variation due to change in column oven temperature
 - ✓ Variation due to change in wavelength
 - ✓ Variation due to change in column lot to lot



Specification

- A specification is a list of test, references to analytical procedures
- Appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described
- Specifications are part of strategy to ensure product quality and consistency



Specification

- Identification
 - ✓ Two methods
- Dissolution
 - ✓ Limits based on initial / stability data
 - ✓ Pharmacopoeial limits, in case official
 - ✓ Reference from OGD or SBA
- Uniformity of dosage units
 - ✓ The dosage form must comply to USP <905>
- Assay
 - ✓ Limits are 90 – 110 % of label claim
 - ✓ Pharmacopoeial limits adopted in case official



Specification

- Related substances
 - ✓ Limits based on daily intake as per ICH guidelines
 - ✓ Any specified degradation product : Qualification limit
 - ✓ Any unspecified degradation product : Identification limit
 - ✓ Total degradation products : Based on data
 - ✓ Pharmacopoeia limits adopted in case official

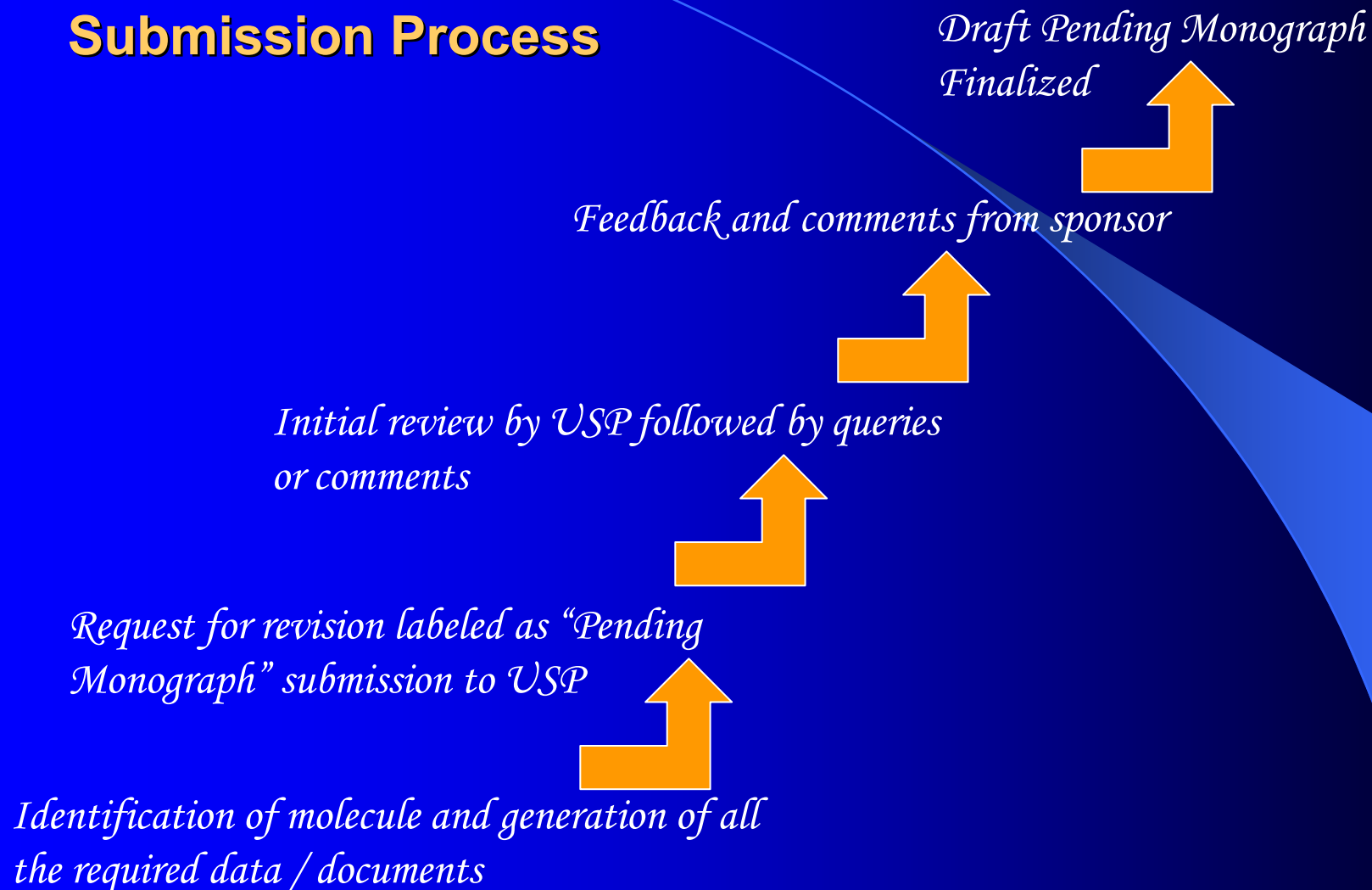


Submission Process



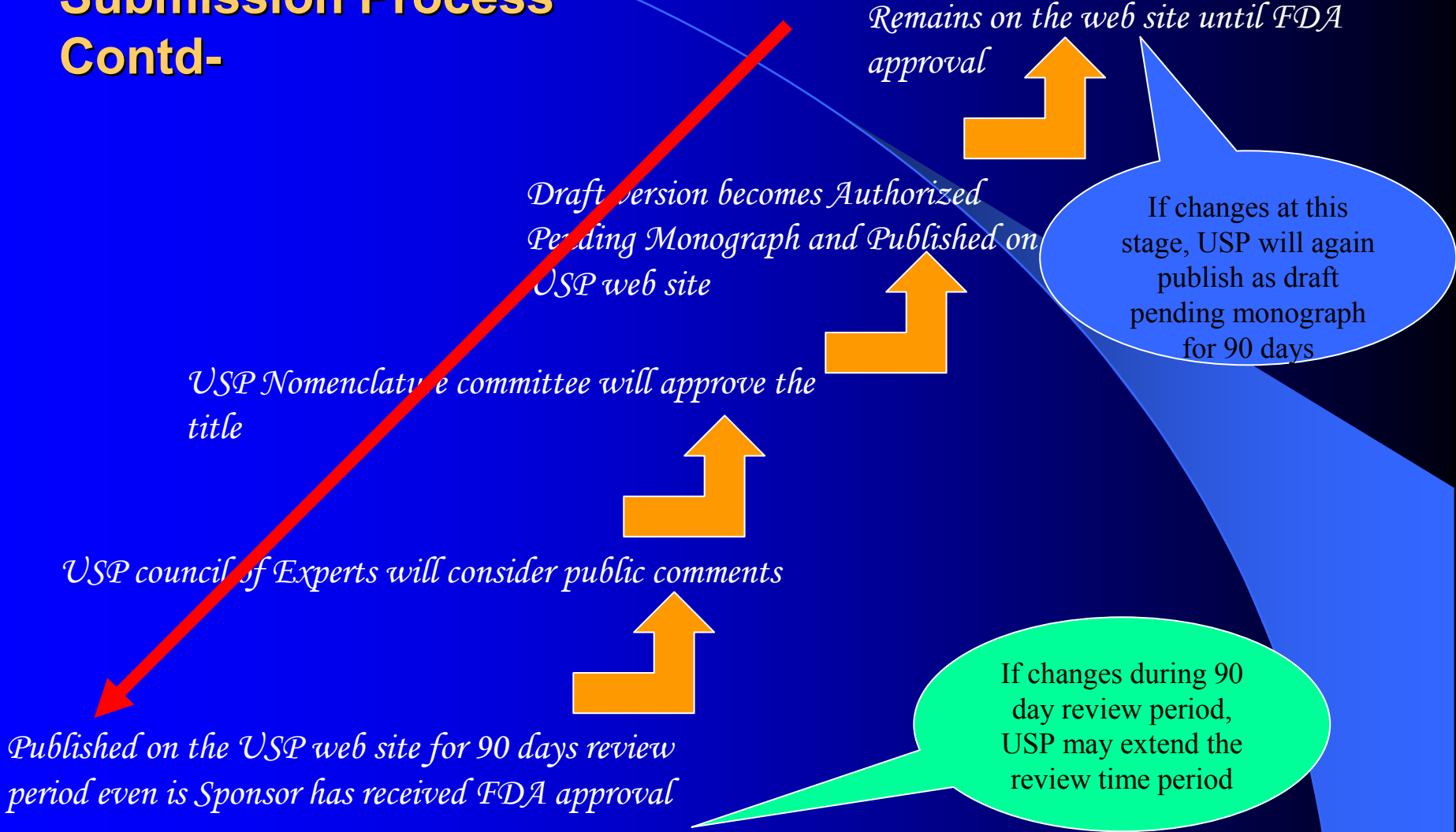
USP Pending Monograph

Submission Process



USP Pending Monograph

Submission Process Contd-



USP Pending Monograph

Submission Process Contd-

Final step is publication of newly official monograph in the next available NF or Supplement

Final approved version of monograph published on USP Web site via a revision Bulletin

If there is an existing official USP monograph, then monograph will be merged to reflect all FDA approved articles

After approval Authorized pending monograph becomes eligible for Official USP Monograph

Monograph is official and legally enforceable as a USP monograph



Thank You

The image features a blue gradient background that transitions from a lighter blue on the left to a darker blue on the right. The text "Thank You" is written in a yellow, cursive script font. The text has a subtle drop shadow effect, making it appear to float above the background. The overall composition is simple and elegant.