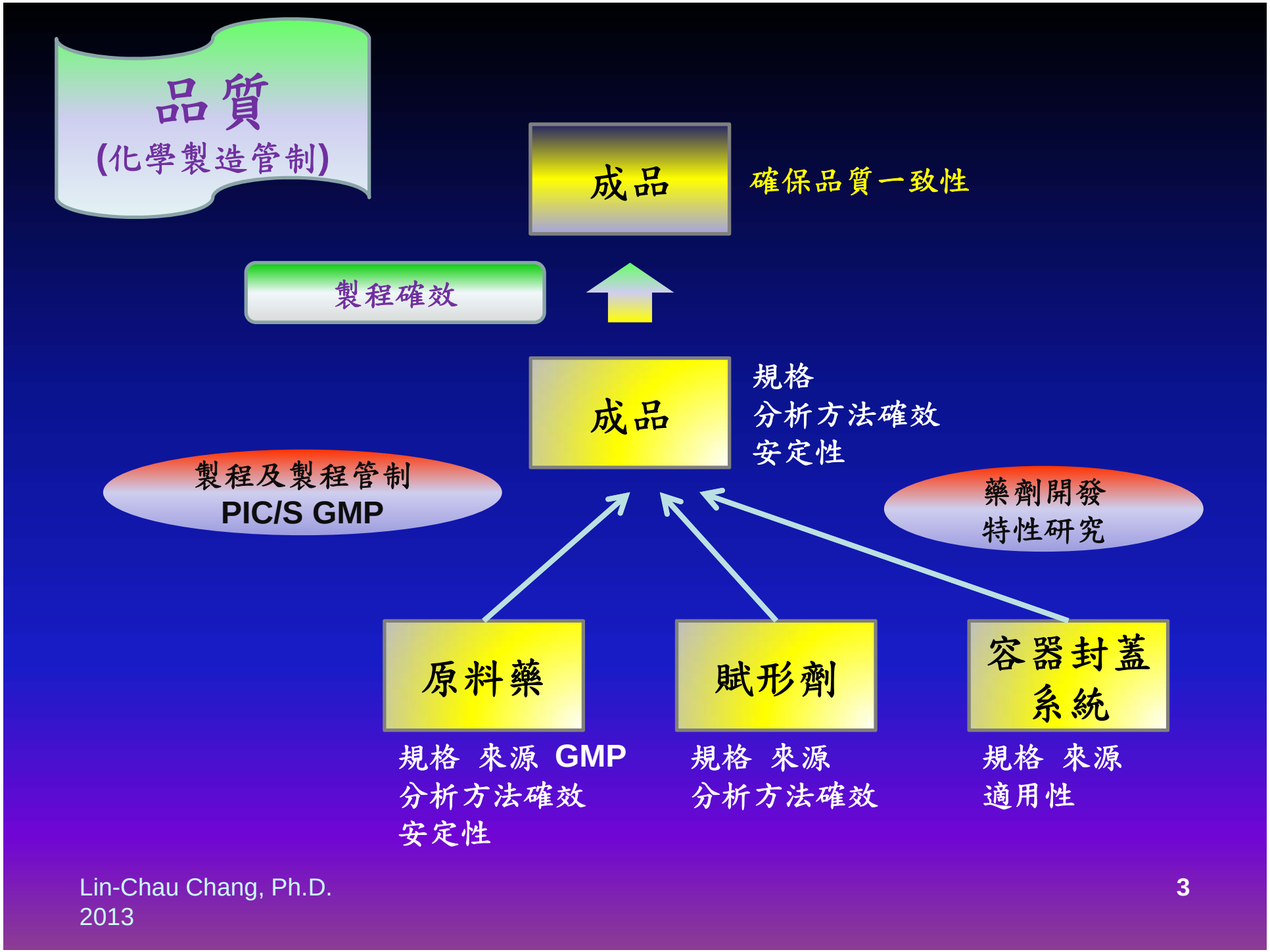
應用通用技術文件格式於學名藥查驗登記-化學製造管制資料送件說明

財團法人醫藥品查驗中心
張琳巧博士/小組長

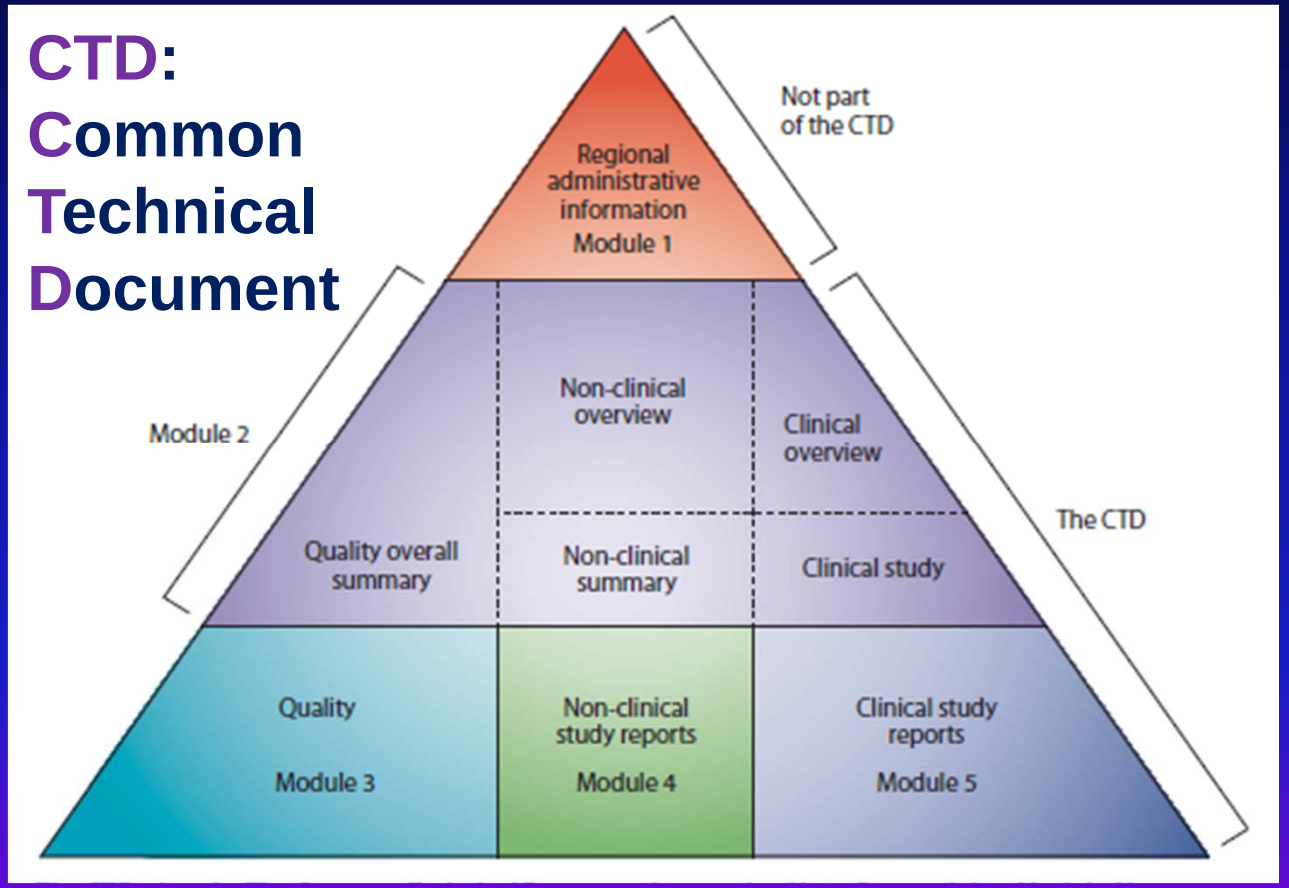
- 本次演講內容僅代表個人觀點
  凡涉及政策方向及法規解釋適用
  應依衛生主管機關之指示為準

- Q: 於CTD格式中所列之文件是否於申請查驗登記時皆須檢附?
  A: CTD格式為申請案件文件編排與呈現之規定方式，各類型藥品所需檢附之行政資料與技術性文件，需參考查驗登記審查準則之規定，行政文件應注意之事項亦可參考「藥品及新興生技藥品組新手上路手冊」及「西藥查驗登記手冊」。


品質
(化學製造管制)
成品
確保品質一致性
製程確效
成品
規格
分析方法確效
安定性
製程及製程管制
PIC/S GMP
藥劑開發
特性研究
原料藥
賦形劑
容器封蓋系統
規格 來源 GMP
分析方法確效
安定性
規格 來源
分析方法確效
規格 來源
適用性

CTD TRIANGLE

CTD:
Common
Technical
Document



Quality

CMC:
Chemistry, Manufacturing and Controls

http://www.ich.org/

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS)

INTRODUCTION

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.A APPENDICES

2.3.R REGIONAL INFORMATION

http://www.ich.org/

MODULE 3: QUALITY

3.1 TABLE OF CONTENTS OF MODULE 3

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.A APPENDICES

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

http://www.ich.org/

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.1 General Information (name, manufacturer)

- ***3.2.S.1.1 Nomenclature (name, manufacturer)***
- ***3.2.S.1.2 Structure (name, manufacturer)***

(The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.**)**

- ***3.2.S.1.3 General Properties (name, manufacturer)***

3.2.S.1.3所須提供之一般性質，資料之詳細程度為何？

有關原料藥之物化性質、相關性質包括其活性，皆須列舉於**3.2.S.1.3**中。若該原料藥可能有多種形式，例如有其他的晶型，並不須列於此章節，在**3.2.S.1.3**內只須列入申請案中所使用之特定晶型，至於其他形式之詳細資料，則應列入**3.2.S.3.1**中。

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3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

是否註明原料藥來源?
是否與藥品查驗登記申請書相符?

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

3.2.S.2.3 Control of Materials (name, manufacturer)

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

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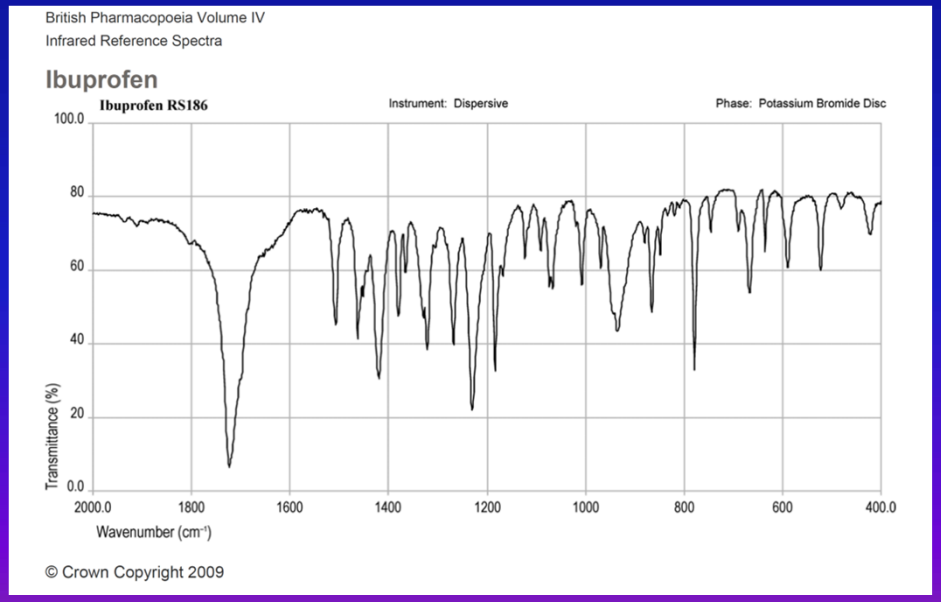
3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

(p.s. Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.)



(e.g. The elucidated structure is consistent with the analytical data obtained from elemental analysis, ultraviolet spectroscopy, infrared spectroscopy, 1H-nuclear magnetic resonance spectroscopy, 13C-nuclear magnetic resonance spectroscopy, mass spectroscopy, X-ray crystallography.)

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

- ***3.2.S.3.2 Impurities (name, manufacturer)***

***ICH: IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2)**

- **Organic impurities (process- and drug-related)**
  - Starting materials
  - By-products
  - Intermediates
  - Degradation products
  - Reagents, ligands and catalysts
- **Inorganic impurities**
  - Reagents, ligands and catalysts
  - Heavy metals or other residual metals
  - Inorganic salts
  - Other materials (e.g. filter aids, charcoal)
- **Residual solvents**

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3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

***ICH: SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES Q6A**

-A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

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3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

Tests	Acceptance criteria	Analytical procedure
Appearance	A white, crystalline powder.	Visual
Identification A: IR B: UV	A. IR: Corresponds to RS B. UV: Absorptivities at xxx nm, do not differ by more than 3.0% from the reference standard.	USP<197M> USP<197U>
Heavy metals	NMT 20 ppm	USP<231>
Assay	98.0-102.0%	USP method
Residual solvents	Methanol: NMT 3000 ppm Methylene Chloride: NMT 600 ppm Toluene NMT 890 ppm	USP <467>
Related Substances	Specified Impurities* RC 1: NMT 0.15% RC 2: NMT 0.25% RC 3: NMT 0.25 % Any unspecified impurity: NMT 0.10% (each) Total impurities: NMT 0.75%	method #41
Polymorphic Form (XRD)	Ratio of peak at 2θ= xx to peak at 2θ=yy: LT 5%	method #47
Particle size (Laser Diffraction)	D90: NMT 30 µm D50: NMT 15 µm D10: NMT 5 µm	method #48

An example of a specification for a drug substance of a solid dosage form (immediate release)

http://www.fda.gov/Drugs/

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

- ***3.2.S.4.2 Analytical Procedures (name, manufacturer)***

  3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

  ***ICH: VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1)**

  -Accuracy, precision, specificity, detection limit, quantitation limit, linearity, range

http://www.ich.org/

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

- ***3.2.S.4.4 Batch Analyses (name, manufacturer)***
- ***3.2.S.4.5 Justification of Specification (name, manufacturer)***

For example:

Residual Solvents	Methanol	NMT 3000 ppm
	Toluene	NMT 890 ppm
	Tetrahydrofuran	NMT 720 ppm
Related Substances	Impurity A:	NMT 0.5%
	Impurity B:	NMT 0.15%
	Impurity C:	NMT 0.15%
	Impurity D:	NMT 0.15%
	Impurity E:	NMT 1.0%
	Impurity F:	NMT 0.50%
	Any Unknown Impurity:	NMT 0.10%
	Total Impurities:	NMT 2.0%

ICH Q3C requirements are met.

A: Metabolite
B, C, D: NMT ICH Q3A qualification threshold (maximum daily dose: 64 mg/day)
E, F: Qualified

Any unknown impurity: NMT ICH Q3A identification threshold

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.5 Reference Standards or Materials (name, manufacturer)

是否提供標準品資料? 檢驗所需之標準品，應註明係**Primary Standard** 或 **Working Standard**。如係**Primary Standard**者，應註明來源；如係**Working Standard**者，應註明來源、批號及標示含量 (或力價)、檢驗規格、檢驗成績書、標定程序。

3.2.S.6 Container Closure System (name, manufacturer)

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

3.2.S.7.3 Stability Data (name, manufacturer)

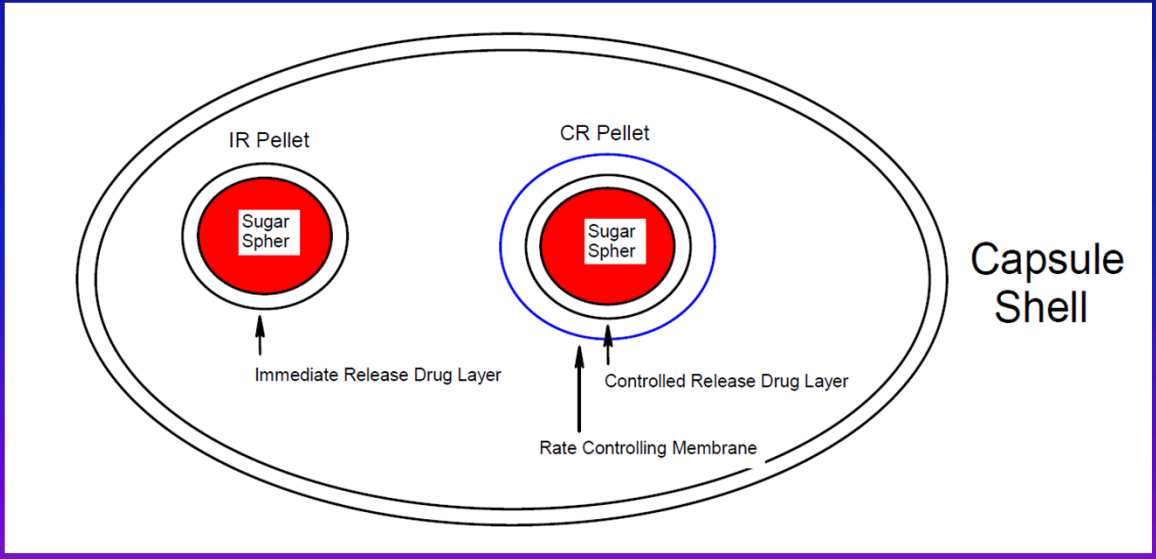
http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

An example-a solid dosage form (controlled release):

The drug product consists of a 1:3 mixture of immediate release (IR) and controlled release (CR) pellets filled into a capsule shell, with each unit capsule containing 32 mg of MK.



http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

An example-a solid dosage form (controlled release)

Ingredient	Function	Weight
Controlled Release (CR) Pellets		
Core		
Sugar Spheres 25-30 mesh	Base	142.5 mg
Drug Layer		
MK	Active	24.00 mg
Clear Coating 732[2]	Binder	28.48 mg
Butylated Hydroxyanisole	Antioxidant/Stabilizer	0.0225 mg
Purified Water[2]	Solvent	
Rate Controlling Membrane		
Ethylcellulose (20 mPa.s)	Rate controlling polymer component	18.00 mg
Triethyl Citrate	Plasticizer	3.000 mg
Purified Water[2]	Solvent	
Total Weight (CR pellets)		216.0 mg
Immediate Release (IR) Pellets[1]		
Core		
Sugar Spheres 18-20 mesh	Base	47.5 mg
Drug Layer		
MK	Active	8.0 mg
Clear Coating 732[1]	Binder	9.49 mg
Butylated Hydroxyanisole	Antioxidant/Stabilizer	0.0075 mg
Purified Water[2]	Solvent	
Total Weight (IR pellets)		65.0 mg
Hard Gelatin Capsule (Size #1)	**Cap and Body**	
Total Fill Weight		281.0 mg

1: Components consist of hypromellose and polyethylene glycol 400

2: Removed during the manufacturing process

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.2 Pharmaceutical Development (name, dosage form)

- ***3.2.P.2.1 Components of the Drug Product (name, dosage form)***
- ***3.2.P.2.1.1 Drug Substance (name, dosage form)***

3.2.P.2.1.1，一般化學藥品需要陳述哪些內容？

須討論原料藥與**3.2.P.1**所列舉之賦形劑的相容性。此外，應討論影響藥品效能之原料藥的關鍵物理化學特性 **(**例如水分含量、溶解度、粒徑分布、多晶型或固相型式 **(polymorphic or solid state form))**。

對於複方 **(combination products)** 應討論各原料藥彼此間的相容性。

例如針對注射劑、眼用製劑、鼻用噴霧劑、吸入劑等劑型之藥品，若所選用賦形劑種類/濃度與第一家核准上市藥品不同者，須討論原料藥與其選用賦形劑之相容性；另，須討論影響藥品效能之原料藥的關鍵物理化學特性。

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.2.1.2 Excipients (name, dosage form)***

有關探討具特殊功能之賦形劑 **(functional excipients)** 於架儲期間所發揮效能之相關資料，應於何章節段落呈現？

具特殊功能之賦形劑如抗氧化劑 **(antioxidants)**、穿透促進劑 **(penetration enhancers)** 等，於架儲期間所發揮效能之相關研究結果，應納入**3.2.P.2.1.2**中。有關防腐劑有效性之探究，則應於**3.2.P.2.5**中說明。

例如針對注射劑、眼用製劑、鼻用噴霧劑、吸入劑等劑型之藥品，若所選用賦形劑種類/濃度與第一家核准上市藥品不同者，須依賦形劑功能討論其選用賦形劑種類、濃度、影響藥品效能之特性。

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.2.2 Drug Product (name, dosage form)***
- ***3.2.P.2.2.1 Formulation Development (name, dosage form)***
- ***3.2.P.2.2.2 Overages (name, dosage form)***

若製程中有增量，須提供評估報告說明其合理性。

- ***3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)***

例如針對注射劑、眼用製劑、鼻用噴霧劑、吸入劑等劑型之藥品，若所選用賦形劑種類/濃度與第一家核准上市藥品不同者，須討論與藥品效能相關之參數如酸鹼值、離子強度、粒徑分布等。

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.2.3 Manufacturing Process Development (name, dosage form)***

Selection

Optimization

Critical aspect

An example-a solid dosage form (controlled release):

	Raw Material	Drug Layering	CR Coating	Encapsulation
Purity	High			
Assay/Content Uniformity		High		High
Release Profile	High		High	High
Stability			High	

若申請資料中須引用非優化之最終製程前所生產批次之數據，須提供相關說明並證明引用之適當性。

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.2.4 Container Closure System (name, dosage form)***

Suitability — **Choice of materials, protection, compatibility**

包裝系統中，有關浸出物及萃出物 (leachables and extractables) 之相關資料，應於何章節段落呈現？

有關浸出物及萃出物 (leachables and extractables) 之相關資料，應於3.2.P.2.4中說明。若有必要，浸出物 (leachables) 部分也應於3.2.P.5.1及3.2.P.5.5中陳述。此外，若在安定性試驗中確認有浸出物 (leachables)，相關結果將於3.2.P.8.3中呈現。

- ***3.2.P.2.5 Microbiological Attributes (name, dosage form)***

For example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.2.6 Compatibility (name, dosage form)***

有關相容性研究之資料，例如凍晶注射劑，於使用前須加入稀釋液配製成注射液，或進一步再調配為輸注液等，探討產品與稀釋液混合之相容性以及安定性等之試驗資料，應於何章節段落呈現？

為了解產品與稀釋液混合之相容性以及安定性等，須進行相關試驗，並將試驗結果列入仿單中，此試驗研究之資料，應於**3.2.P.2.6**中說明。若此試驗資料乃正式安定性試驗 **(formal stability studies)** 中之一部分，相關結果將於**3.2.P.8.3**中呈現。

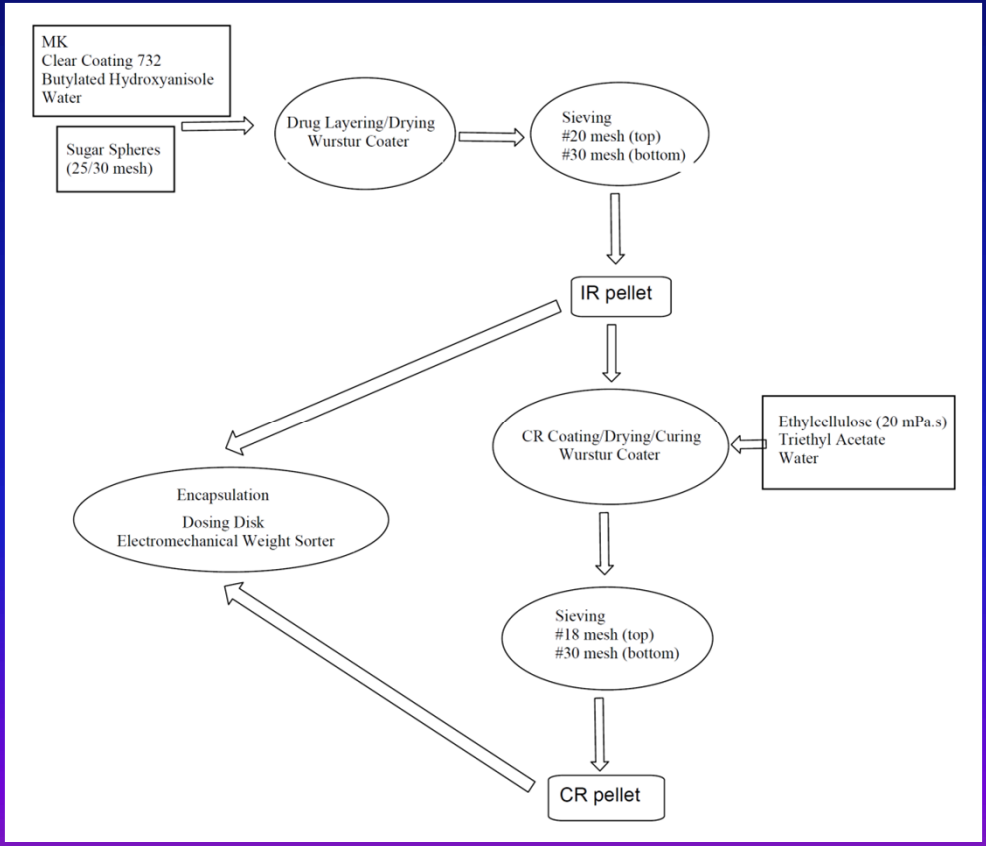
3.2.P.3 Manufacture (name, dosage form)

- ***3.2.P.3.1 Manufacturer(s) (name, dosage form)***
- ***3.2.P.3.2 Batch Formula (name, dosage form)***

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)



For example-a solid dosage form (controlled release)

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.3.3製程及製程管制之描述部分，一般化學藥品需要陳述哪些內容？

應以流程圖呈現產品製程之步驟，且能顯示各組成成分/物料於何步驟加入製程中。同時，須指出關鍵步驟及進行製程管制、中間產物測試、最終產品管制等之時間點。此外，應提供製程步驟 (包含包裝過程) 執行順序及生產規模之描述。直接影響產品品質之新穎製程或技術以及包裝操作等，應進一步詳加描述。相關設備部分至少須指出類型 (例如滾動式混合機 (tumble blender)、線內均質機 (in-line homogeniser)) 及作業產能。製程步驟亦須說明適當製程參數，例如，時間、溫度或酸鹼值，且配合數值呈現預期範圍。關鍵步驟所訂定之數值範圍合理性應在3.2.P.3.4中說明。某些狀況下，應陳述其環境條件 (例如對於發泡產品 (effervescent product) 之低濕度說明)。對於物質重處理之預定計畫應證明其合理性，而支持該合理性之數據資料應在此章節 (3.2.P.3.3) 中以交互參照之方式引用或直接彙整呈現。

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)***

  For example-a solid dosage form (controlled release):

  Critical step: Drug layering

In-Process Test	Acceptance Criteria
Description	White to slightly off-white spherical beads
Assay	95.0-105.0% of theoretical drug content (123 mg MK/g of IR pellet)
Uniformity of Dosage Units	Mean 90-110%, RSD NMT 5% (Pellet equivalent of 96 mg of MK)
Pellet Size	D_{50}: NMT 730 µm D_{90}: NMT 780 µm
Moisture	NMT 2.0%

- ***3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)***

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.4 Control of Excipients (name, dosage form)

- ***3.2.P.4.1 Specifications (name, dosage form)***
- ***3.2.P.4.2 Analytical Procedures (name, dosage form)***
- ***3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)***
- ***3.2.P.4.4 Justification of Specifications (name, dosage form)***
- ***3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)***
- ***3.2.P.4.6 Novel Excipients (name, dosage form)***

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

For example:

Compendial excipients:

Ingredient	Manufacturer	Complies with USP/NF Tests
Sugar Spheres NF, 25/30 mesh*	Sugar Inc.	Yes
Triethyl Citrate NF	Plasticizer Inc.	Yes
Butylated Hydroxyanisole NF	Antioxidant Inc.	Yes
Purified Water USP	In-House	Yes

Ingredient	Manufacturer	Complies with USP/NF Tests
Ethylcellulose NF (20 mPa.s)	Control Release Inc.	Yes
Specifications Beyond Pharmacopeial Standards		
Test	Limits	Result
Ethoxy Content (N-Type)	48.0.0-49.5%	48.8%
Viscosity	18.0 – 22.0 mPa.s	20.1 mPa.s

The impact of viscosity on release: huge!

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

Are critical drug product attributes included?

Is there any monograph for the drug product listed in pharmacopoeias (ChP/10 advanced countries; edition published within 5 years)?

Are residual solvents tested? Are formulation-related test items included?

ICH Q6A

ICH Q3B(R2)

3.2.P.5.2 Analytical Procedures (name, dosage form)

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

ICH Q2(R1)

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- ***3.2.P.5.4 Batch Analyses (name, dosage form)***
- ***3.2.P.5.5 Characterisation of Impurities (name, dosage form)***
- ***3.2.P.5.6 Justification of Specification(s) (name, dosage form)***
- **3.2.P.6 Reference Standards or Materials (name, dosage form)**

3.2.P.6與3.2.S.5皆是對照標準品或對照物質之說明，是否若在3.2.S.5已列，則不須於3.2.P.6中重複列出？

在3.2.P.6之段落中，若有資料已列於3.2.S.5中，則得以交互參照方式之方式引用，但其餘所有對照標準品或對照物質之資料，例如僅用於分析成品時使用者，皆須列於3.2.P.6中。

- **3.2.P.7 Container Closure System**

http://www.ich.org/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

Tests	Acceptance Criteria	Analytical Procedure
Description	No. 1 blue green opaque cap/yellow opaque body hard shell gelatin capsule filled. The capsule is axially printed with "MK" over "32' in white ink on both the cap and body.	Visual
Appearance	No observation of discoloration, softening, stickiness brittleness, or cracking	Visual
Identification	1. HPLC: The retention time of the major peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	In-House HPLC Test Method #125b
	2. UV: Spectrum corresponds to that of corresponding preparation of the reference standard	In-House HPLC (PDA Detector) Test Method #125b
Drug Release	Time % Dissolved 0.5 hr: Between 25-35% 4 hr: Between 40-60% 8 hr Between 65-85% 12 hr: NLT 85%	Medium: 900 mL, 0.05 M Phosphate Buffer (pH 6.8) at 37 °C. Apparatus: 1 (basket) at 100 rpm
Uniformity of Dosage Units	USP <905>	In-House HPLC Test Method #125c
Assay	95.0-105.0%	In-House HPLC Test Method #125b
Degradation Products	Impurity A: NMT 1.5% Impurity E: NMT 1.0% Any Unknown Impurity: NMT 0.2% Total Impurities: NMT 2.5%	In-House HPLC Test Method #231b
Moisture	NMT 3.5%	Karl Fischer Titration (USP <921> Method 1a)

An example of a specification for a drug product of a solid dosage form (controlled release)

http://www.ich.org/
http://www.fda.gov/Drugs/

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.8 Stability (name, dosage form)

- ***3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)***
- ***3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)***
- ***3.2.P.8.3 Stability Data (name, dosage form)***

Is the specification appropriate?

Are the stability studies conducted on the drug products packaged with the intended container closure system?

Is the protocol appropriate?
Do studies and results support the storage conditions and usage?

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3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

- 3.2.A Appendices
- 3.2.A.1 Facilities and Equipment (name, manufacturer)
- 3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)
- 3.2.A.3 Excipients
- 3.2.R Regional Information
- 3.2.R.1 Master Production and Control Records (including bill of materials in batch record) or Batch Record
- 3.3 Literature References

http://www.ich.org/

REFERENCES/USEFUL LINKS

- 衛生署食品藥物管理局資料庫查詢
  http://www.fda.gov.tw/TC/site.aspx?sid=38
- 台灣藥物法規資訊網
  http://regulation.cde.org.tw/
- **EDQM**
  http://www.edqm.eu/en/Databases-10.html
- **EMA website**
  http://www.emea.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true

REFERENCES/USEFUL LINKS

- **ICH**
  http://www.ich.org/
- **US FDA website**
  http://www.fda.gov/
  -US FDA guidances
  http://www.fda.gov/Drugs//guidancecomplianceregulatoryinformation/guidances/default.htm
  -Database
  http://www.fda.gov/Drugs//InformationOnDrugs/default.htm
  -DMF
  http://www.fda.gov/Drugs//DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

Thank you very much for your attention!