製藥工廠基本資料Site Master File (SMF)製備說明

EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE

PE008-4　1 Annex (1 January 2011)

行政院衛生署

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序

為強化藥物製造業者之管理，並與國際規範接軌，本署參考國際作法，規定製藥工廠應製備「工廠基本資料Site Master File (SMF) 」（以下簡稱SMF），供本署執行各項檢查作業前，瞭解製藥工廠之最新概況，以作有效之規劃與安排。本署前藥物食品檢驗局曾於91年6月10日以藥檢科字第9109647號函公布製備「工廠基本資料Site Master File (SMF) 」之說明備忘錄。該備忘錄係參照1993年PIC/S組織公布之「EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE」翻譯而成。該組織於2011年1月1日公布新版之SMF，主要新增有關品質風險評估政策之相關要求，本次係參照該版本修正SMF製備說明內容。

SMF 內容應包含廠內各項資料，但盡可能不超過 25 到 30 頁（附錄另加），並以簡要計畫、大綱圖示或圖解編排方式，取代使用敘述的方式，另其附件若使用 A4 紙張列印時，亦應清楚可讀。此外，工廠基本資料應列屬於廠內品質管理系統文件的一部份，該份文件應有版本編號、審核日期及生效日期，並應定期進行審閱以確保該文件為最新版本。

SMF 應包含廠內之品質管理策略及各項作業等之特定資訊，若廠內僅執行部分之藥品生產作業，例如：僅有包裝作業時，則僅需描述該作業。另，本說明內容適用於所有類型之製造作業，例如：藥品之生產、包裝、貼標、檢驗、重貼標及重包裝等。

本說明內容以中英文對照方式呈現，製藥工廠應依該新版格式製備廠內之 SMF。未來，PIC/S 組織若有更新時，本署亦將配合隨時更新並公布週知。

工廠基本資料內容 (CONTENT OF SITE MASTER FILE)

1. 製造廠基本資料 (GENERAL INFORMATION ON THE MANUFACTURER)	
1.1 製造廠聯絡資料	1.1 Contact information on the manufacturer
- 製造廠名稱及正式地址；	- Name and official address of the manufacturer;
- 工廠名稱及地址，廠區內各建築與生產單位之位置；	- Names and street addresses of the site, buildings and production units located on the site;
- 當有產品瑕疵或回收時，製造廠的聯絡資訊，包括聯絡人員 24 小時的聯絡電話；	- Contact information of the manufacturer including 24 hrs telephone number of the contact personnel in the case of product defects or recalls;
- 工廠之識別碼，如 GPS (全球定位系統) 資訊或任何其他地理定位系統。 - 工廠登記字號。	- Identification number of the site as e.g. GPS details or any other geographic location system. - Certification number of the site.
1.2 工廠經核准之藥品製造作業	1.2 Authorised pharmaceutical manufacturing activities of the site
- 附件 1 附上主管機關核發且仍在效期內之製造許可影本。若主管機關未核發製造許可時，亦應註明；	- Copy of the valid manufacturing authorisation issued by the relevant Competent Authority in Appendix 1. If the Competent Authority does not issue manufacturing authorisations, this should be stated;
- 簡述未納入製造許可但由相關主管機關 (包括國外機關) 核准之各種劑型/作業的製造、輸入、輸出、運銷及其他項目；	- Brief description of manufacture, import, export, distribution and other activities as authorised by the relevant Competent Authorities including foreign authorities with authorised dosage forms/activities, respectively; where not covered by the manufacturing authorisation;
- 列述不包含在附件 1 由該廠製造的產品類型 (列舉於附件 2)；	- Type of products currently manufactured on-site (list in Appendix 2) where not covered by Appendix 1;
- 列舉工廠最近 5 年內接受 GMP 稽查之清單，包括日期及執行稽查之主管機關	- List of GMP inspections of the site within the last 5 years; including dates

名稱/國家。將現行 GMP 證明書影本置於附件 3。	and name/country of the Competent Authority having performed the inspection. A copy of current GMP certificate (Appendix 3) should be included, if available.
1.3 廠內其他之製造作業	1.3 Any other manufacturing activities carried out on the site
- 描述廠內任何非藥品之作業。	- Description of non-pharmaceutical activities on-site, if any.
2. 製造廠之品質管理系統 (QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER)	
2.1 製造廠之品質管理系統	2.1 The quality management system of the manufacturer
- 簡述公司內運作之品質管理系統及其所參照之標準；	- Brief description of the quality management systems run by the company and reference to the standards used;
- 有關維持品質系統之相關職責說明，包括高層管理者之職責；	- Responsibilities related to the maintaining of quality system including senior management;
- 廠內被認可及認證作業之資訊，包括認證的日期及內容，以及認證機構名稱。	- Information of activities for which the site is accredited and certified, including dates and contents of accreditations, names of accrediting bodies.
2.2 最終產品之放行程序	2.2 Release procedure of finished products
- 詳述負責批次核定與放行程序之被授權人員/合格人員之資格要求 (教育背景與工作經驗)；	- Detailed description of qualification requirements (education and work experience) of the Authorised Person(s) / Qualified Person(s) responsible for batch certification and releasing procedures;
- 敘述批次核定與放行程序；	- General description of batch certification and releasing procedure;
- 在最終產品待驗與放行，以及評估是否符合上市許可中，被授權人員/合格人員所擔任之角色；	- Role of Authorised Person / Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation;
- 若廠內有多位被授權人員/合格人員	- The arrangements between Authorised

時，他們的職責區分；	Persons / Qualified Persons when several Authorised Persons / Qualified Persons are involved;
- 敘明管制策略是否採用製程分析技術 (PAT) 及/或即時放行或參數放行。	- Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release.
2.3 供應商及合約商之管理	2.3 Management of suppliers and contractors
- 簡要彙整供應鏈體系之建立/資訊，以及外部稽核計畫；	- A brief summary of the establishment/knowledge of supply chain and the external audit program;
- 簡述合約商、原料藥 (API) 製造業者與其他關鍵性原物料供應商之資格認可系統；	- Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical materials suppliers;
- 為確保所製造之產品符合 TSE (傳染性動物海綿狀腦病) 指引所採取之措施；	- Measures taken to ensure that products manufactured are compliant with TSE (Transmitting animal spongiform encephalopathy) guidelines;
- 用以發覺或辨識產品、半製品 (如尚未包裝之錠劑)、原料藥或賦型劑等被仿冒/造假的措施；	- Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified;
- 相關的製造與檢驗使用廠外科學、分析或其他技術支援；	- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- 列出委託製造業者與實驗室清單，包括其地址與委託資訊，亦包括委外製造與品質管制作業供應鏈的流程圖，例如：無菌製備所使用之直接包裝材料的滅菌、起始原料之檢驗等，將上述資料呈現於附件4；	- List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply-chains for outsourced manufacturing and Quality Control activities; e.g. sterilisation of primary packaging material for aseptic processes, testing of starting raw materials etc, should be presented in Appendix 4;
- 簡述委託者與受託者間在符合上市許	- Brief overview of the responsibility

可所各自分擔的責任 (對於未納入在 2.2 中的部份)。	sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorisation (where not included under 2.2).
2.4 品質風險管理	2.4 Quality Risk Management (QRM)
- 簡述製造業者所使用的品質風險管理方法；	- Brief description of QRM methodologies used by the manufacturer;
- 品質風險管理之範圍與重點，包括簡述在母公司階層所實施以及在各子公司所實施的任何作業。應提及品質風險管理系統的任何應用，以評估供應品的一致性。	- Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.
2.5 產品品質檢討	2.5 Product Quality Reviews
- 簡述所使用的方法。	- Brief description of methodologies used.
3. 人事 (PERSONNEL)	
- 將標明品質管理、生產、品質管制之職位/職稱的組織圖置於附件5，包括高階管理者與被授權人員/合格人員；	- Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 5, including senior management and Authorised Person(s) / Qualified Person(s);
- 分別從事品質管理、生產、品質管制、倉儲及運銷的員工人數。	- Number of employees engaged in the quality management, production, quality control, storage and distribution respectively.
4. 廠房設施及設備 (PREMISES AND EQUIPMENT)	
4.1 廠房設施	4.1 Premises
- 簡述工廠，包括廠區之面積及各棟建築物清單。若生產作業係針對不同市場需求而在廠區內不同建築物執行時，例如針對國內、歐盟、美國等，則應列出各棟建築物之標的市場 (若在 1.1 項沒有加以區分時)；	- Short description of plant; size of the site and list of buildings. If the production for different markets, i.e. for local, EU, USA, etc. takes place in different buildings on the site, the buildings should be listed with destined markets identified (if not identified under 1.1);
- 簡圖或附有比例尺之製造區域的描述 (不需建築圖或工程圖)；	- Simple plan or description of manufacturing areas with indication of

	scale (architectural or engineering drawings are not required);
- 生產區域之配置及流程圖 (見附件 6) 顯示各房間的潔淨度分級與鄰近區域的壓差，並標示房間內之作業項目(例如調製、充填、儲存、包裝等)；	- Lay outs and flow charts of the production areas (in Appendix 6) showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms;
- 倉庫與儲存區域之配置，如有高毒性、危害性及致敏性之原物料時，應標示其儲存與處理的特定區域；	- Lay-outs of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitizing materials indicated, if applicable;
- 若未在前述平面圖上標示時，則應簡述其特定的儲存條件。	- Brief description of specific storage conditions if applicable, but not indicated on the lay-outs.
4.1.1 簡述空調 (HVAC) 系統	4.1.1 Brief description of heating, ventilation and air conditioning (HVAC) systems
- 簡述空氣供應、溫度、濕度、壓差、換氣數及空氣再循環率 (%) 策略之訂定原則。	- Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%).
4.1.2 簡述水系統	4.1.2 Brief description of water systems
- 產製用水的品質參考依據。	- Quality references of water produced;
- 附件 7 附上水系統之圖示。	- Schematic drawings of the systems in Appendix 7.
4.1.3 簡述其他相關公用設施，例如蒸汽、壓縮空氣、氮氣等。	4.1.3. Brief description of other relevant utilities, such as steam, compressed air, N2, etc.
4.2 設備	4.2 Equipment
4.2.1 附件 8 提供主要生產與品管實驗室設備之清單，並標示出設備的關鍵性部分	4.2.1 Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Appendix 8
4.2.2 清潔與衛生	4.2.2 Cleaning and sanitation
- 簡述與產品有接觸的設備表面之清潔	- Brief description of cleaning and

與衛生處理方法 (例如，手工清潔、自動就地清潔等)。	sanitation methods of product contact surfaces (i.e. manual cleaning, automatic Clean-in-Place, etc).
4.2.3 GMP 相關之電腦化系統	4.2.3 GMP critical computerised systems
- 描述與 GMP 有重要相關之電腦化系統 (設備上特定性之可程式邏輯控制器 (PLCs) 除外)。	- Description of GMP critical computerised systems (excluding equipment specific Programmable Logic Controllers (PLCs).
5. 文件 (DOCUMENTATION)	
- 描述文件系統 (例如，電子文件、紙本文件)；	- Description of documentation system (i.e. electronic, manual);
- 當文件及紀錄 (包括合適時藥物安全監視數據) 係儲存或歸檔於廠外時：列出該文件/紀錄之類型、儲存地點之名稱與地址，以及估計從廠外取回文件所需之時間。	- When documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): List of types of documents/records; Name and address of storage site and an estimate of time required retrieving documents from the off-site archive.
6. 生產 (PRODUCTION)	
6.1 產品之類型 (可參考附件 1 與附件 2)：	6.1. Type of products (references to Appendix 1 or 2 can be made):
- 所製造產品之類型，包括；	- Type of products manufactured including;
* 廠內製造之人用及動物用藥品劑型之清單；	* list of dosage forms of both human and veterinary products which are manufactured on the site;
* 廠內為任何臨床試驗所製造的研究用藥品 (IMP) 之劑型清單，當其製造場所與人員及上市產品之製造場所與人員不同時，則應有這些場所與人員的資訊；	* list of dosage forms of investigational medicinal products (IMP) manufactured for any clinical trials on the site, and when different from the commercial manufacturing, information of production areas and personnel;
- 具有毒性或危害性物質之處理方法 (例如，具高藥理活性及/或具致敏性之特性者)；	- Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitising properties);
- 若以專用設施或以時段切換生產為基礎的方式所製造之產品類型，則應予以	- Product types manufactured in a dedicated facility or on a campaign

敘明；	basis, if applicable;
- 若採用製程分析技術 (PAT)：則概述其相關技術及所連結之電腦化系統。	- Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology, and associated computerized systems.
6.2 製程確效	6.2 Process validation
- 簡述製程確效之一般策略；	- Brief description of general policy for process validation;
- 重處理或再加工之策略。	- Policy for reprocessing or reworking.
6.3 原物料管理及倉儲	6.3 Material management and warehousing
- 原料、包裝材料、待分包裝產品及最終產品處理的安排，包括抽樣、待驗、放行及儲存；	- Arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage;
- 拒用原物料及產品處理的安排。	- Arrangements for the handling of rejected materials and products.
7. 品質管制 (QUALITY CONTROL)	
- 描述廠內在物理、化學、微生物學及生物學試驗方面所執行的品質管制作業。	- Description of the Quality Control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing.
8. 運銷、申訴、產品瑕疵及回收 (DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS)	
8.1 運銷(針對製造業者所負的責任)	8.1 Distribution (to the part under the responsibility of the manufacturer)
- 產品出貨的對象 (持有批發商許可者，持有製造許可者等) 及其地點 (歐盟/歐洲經濟區、美國等)；	- Types (wholesale licence holders, manufacturing licence holders, etc) and locations (EU/EEA, USA, etc.) of the companies to which the products are shipped from the site;
- 所使用系統的描述，以確認每一客戶/接收者係合法取得該製造業者所製造的藥品；	- Description of the system used to verify that each customer / recipient is legally entitled to receive medicinal products from the manufacturer;
- 簡述在運送期間確保在適當環境條件下的系統，例如，溫度監控/管控；	- Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature

	monitoring/ control;
- 產品運銷的安排及維持產品可被追溯的方法；	- Arrangements for product distribution and methods by which product traceability is maintained;
- 防止製造業者之產品淪為非法供應鏈所採取的措施。	- Measures taken to prevent manufacturers' products to fall in the illegal supply chain.
8.2 申訴，產品瑕疵及回收	8.2 Complaints, product defects and recalls
- 簡述處理申訴、產品瑕疵及回收的系統。	- Brief description of the system for handling complains, product defects and recalls.
9. 自我查核 (SELF INSPECTIONS)	
- 簡述自我查核系統，並將重點放在訂定查核計畫時查核範圍的選擇標準、實務安排及後續跟催行動。	- Short description of the self inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

附件

附件 1　效期內的製造許可影本。	Appendix 1　Copy of valid manufacturing authorization.
附件2　製造劑型之清單，包括所用原料藥之INN-名稱或一般名稱 (可行時)。	Appendix 2　List of dosage forms manufactured including the INN-names or common name (as available) of active pharmaceutical ingredients (API) used.
附件 3　效期內的 GMP 證明書影本。	Appendix 3　Copy of valid GMP Certificate.
附件4　委 (受) 託製造業者與實驗室之清單，包括其住址、聯絡方式，以及這些委(受) 託作業供應鏈之流程圖。	Appendix 4　List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply chains for these outsourced activities.
附件 5　組織圖	Appendix 5　Organisational charts.
附件 6　生產區配置圖，包括物流及人流，每一產品類型 (劑型) 的製造作業流程圖。	Appendix 6　Lay outs of production areas including material and personnel flows, general flow charts of manufacturing processes of each product type (dosage form).
附件 7　水系統圖示。	Appendix 7　Schematic drawings of water systems.
附件 8　主要的生產及實驗室設備清單。	Appendix 8　List of major production and laboratory equipment.