「目標產品概況」撰寫提示
Target Product Profile（TPP）

生醫商品化中心
BioMed Commercialization Center

生醫商品化中心|藥品領域
案源評估組|PM組
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Jan. 23, 2019

科技部生命科學研究發展司

一、基本資

計畫型	
疾病領域 (單選，請選擇)	
全程執行	
申請機	
計畫主	
計畫名稱	
計畫屬	
產品/技術 (單選，請選擇)	
計畫主持	
其他聯絡	
通訊地	

計畫申請人

二、目標產品概況表 (Target Product Profile) (請依申請案之產品/技術屬性，選擇合適之表格填寫，並依需要調整欄寬；目前無實驗數據或不適用之欄位，請填 NA。)

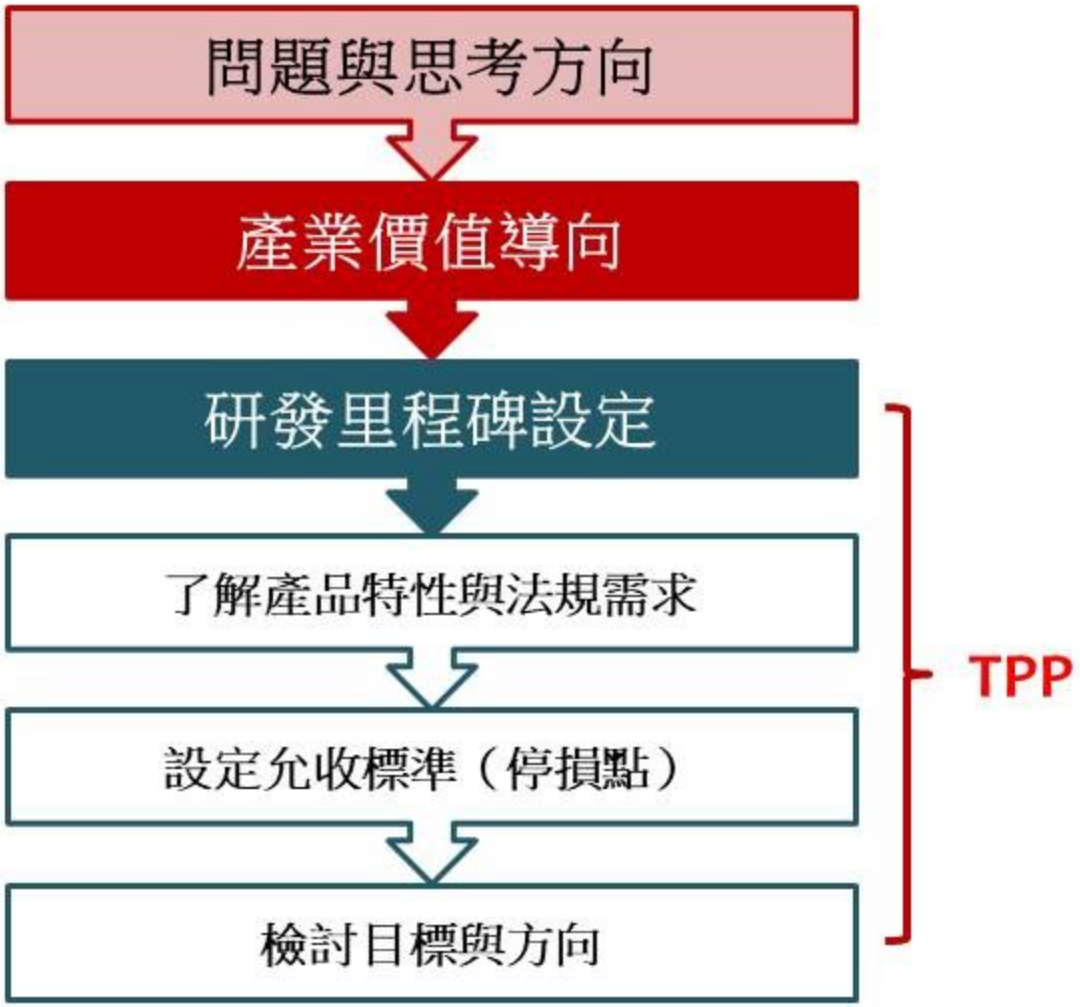
藥品	
Item	
Target Indications or usage	
Mechanism	
Route of Administration	
Product Formulation	
Dose Schedule	
Safety	
Efficacy	
Nonclinical Toxicolog	
Biomarkers	
Product Presentation and Storage	
Drug Interactions	
Adverse Reactions	
Intellectual Property	

三、計畫內容 (篇幅以不超過 10 頁為原則)

1. 計畫目的：請描述本計畫之確切目標(specific aims)及研究重點。(半頁為宜)
2. 研發背景：撰寫重點為此研發計畫預期產出之產品/技術所欲解決之醫療需求，及與現有標準療法或或開發中產品/技術相較，其優異或獨特處。(1 頁為宜)
3. 研發標的：小分子者，請提供其名稱、分子式、結構（或架構類型）；蛋白質或核酸者，請提供其名稱、序列。若為天然萃取物，請說明萃取方法及步驟；如涉及新製程，請說明合成方法並圖示步驟。(1 頁為宜)
4. 研發現況：概述此研發計畫之關鍵試驗數據及結果，並請強調藥效數據。(5 頁為宜)
5. 研發規劃：請具體說明規劃之工作項目及執行者(如，由資源中心、或委託廠商進行)；並於下表中，以甘特圖示意各工作項目之預期進程及 go-no go decision point。(1.5 頁為宜)
6. 預期效益：請簡述預期產出之產品/技術之臨床安全與功效、病人福祉、成本分析和具體預期效益等。(1 頁為宜)

年 / 研發階段/工作項目	第 1 年				第 2 年			
A.								
A1.			■	■				
A2.				■				
A3.			■	■				
B.								
B1.								
B2.								

育苗計畫--產業價值為導向的新藥研發計畫



https://goo.gl/images/coUXH4

新藥開發導航利器

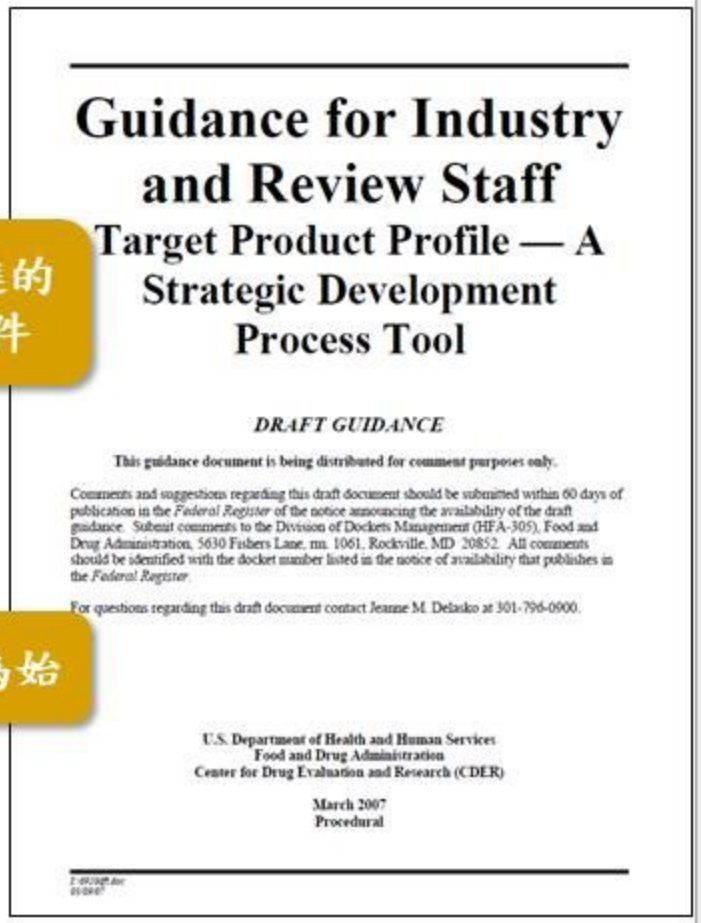
目標產品概況
TARGET PRODUCT PROFILE (TPP)

Target Product Profile (TPP)

- 藥物開發整體計畫的摘要--以藥品仿單（labeling）事項為範圍（FDA, 2007）
  - Submission to FDA is voluntary
- a "living document" --a dynamic summary
  - 需隨研發進展及市場環境變化（e.g. 競爭環境）不斷更新
- Beginning with the goal in mind
  - 從最終產品端（臨床使用情境）反推開發步驟
- 由參與研發的跨領域團隊共同制定

與時俱進的動態文件

以終為始



Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

TPP 功能

- 可凝聚跨領域團隊共識，聚焦計畫執行目標
  - 團隊共同負責，朝向一致目標前進，而非各做各的
- 新藥開發溝通平台
  - 跨領域單位之間的共通語言：公司內部、法規單位、投資人
  - 提升溝通效率
- 專案管理與投資決策工具
  - 依據TPP設定的目標，擬定研發項目優先次序、增減試驗項目
  - 在TPP預先設定里程碑及go/no-go條件，隨時更新市場最新資訊、競爭者動態，利於決策者進行資源配置、風險評估或營運決策之參考

撰寫TPP應思考的問題

捫心自問

- Indication: 我的藥物用來治療甚麼疾病？
- Population: 我的藥物用來治療甚麼樣的病人？
- Standard-of-care: 目標適應症的標準療法是甚麼？
- Differentiation: 我的藥物比標準療法好在哪裡？療效或安全性？
- Competitive landscape: 競爭對手是甚麼？我的藥物是否有差異化競爭優勢？
- Route of administration: 我的藥物如何使用在病人身上？
- Dosing frequency: 多久給藥一次？用藥時間多長？
- Stability: 藥物保存條件與安定性如何？
- Cost: 病人是否負擔得起？健保是否可能給付？
- Time to availability: 我的藥物預計何時可以上市？階段性研發目標為何？研發期多長？
- Factors for success:有多少成功把握？團隊的核心能力為何？不足能力為何？
- Consequences for no-go: 萬一目標無法達成的後果為何？有無B計畫？

TPP Template --屬性與目標設定

育苗計畫提案書 TPP –藥品

屬性	Item	Target Profile	Current Status
科學	Target Indications or usage		
	Mechanism		
	Route of Administration		
	Product Formulation		
	Dose Schedule		
	Safety		
	Efficacy		
	Nonclinical Toxicology		
	Biomarkers		
	Drug Interactions		
	Adverse Reactions		
商業	Product Presentation and Storage		
	Intellectual Property		

最終產品的目標值

- 可接受範圍（Base-case）
  - 參考競爭藥物的產品資訊，設定可接受最低標準
- 最佳範圍（Ideal profile）
  - 依本產品研發潛力，預估可能達到之最佳目標

- 依產品特性及研發階段選擇合適的屬性
- Labeling concepts + business consideration

US FDA TPP --Labeling concepts

- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Overdosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information

TPP- Target Product Profile

Financial considerations	**Basic economics: ROI, NPV** • **Affordability to end user** • **Cost of goods** • **Projected pricing** • **Cost to develop** • **Partners**
Intellectual property	Path forward • Freedom to operate • Patentability
Regulatory considerations	Presumed path forward • Eligibility for Orphan drug status, Fast Track, Subpart H • Are there clear precedents

TPP Template

NO	Description	Comparator Label	Base Case	Upper Case
	Project Name	**Compound X**		
	Target Class			
	Compound Class			
	Comparator (targeted benchmark drug)			
1	Therapeutics Area			
2	Indication			
3	Target population			
4	Dosage/form / Route of Administration			
5	Dose (frequency)			
6	Formulation and Dosing Regimen			
7	Phill burden (optional)			
8	Durability (API Half Life T1/2)			
9	Safety/Tolerability			
10	Efficacy			
11	Palatibility			
12	Stability			
13	Cost of Goods			
14	Price (£ per day) and qualification of pricing strategy			
15	Contraindications/ warnings/ precautions (including Side Effect/Class warning)			
16	DDI/Contradiction			
17	Food-Drug Interaction			
18	Target Label			
19	Clinical Efficacy			
20	Orphan Drug Designation (ODD)			
21	IP Status			
22	Competitive Environment			

業界使用範本

- 依產品特性及研發階段選擇合適的屬性
- Labeling concepts + business consideration

第一次寫TPP就上手

找出可能發展的適應症

- 考量 Target/MOA/drug class

決定一個適應症

- 考量市場需求（unmet medical need）、競爭力分析（強調差異化優勢）、開發可行性（**POC**、專利、法規）
- 徵詢臨床KOL意見

i.e. 選題考量
- ✓ Unmet medical need
- ✓ 差異化優勢
- ✓ 開發可行性

選定競爭藥物（comparator）

- 根據所選定的適應症
- 參考現行標準療法、未上市研發產品之已發表的臨床試驗數據

建立TPP

- 依研發里程碑設定產品研發屬性（attributes）及允收標準（criteria）
- 參考競品仿單設定最低可接受範圍（base-case）或最佳目標範圍（Ideal profile）
- 填入研發產品的已知資訊

開始使用

- 日常研發討論
- PM會議
- Milestone review
- Go/no-go decision

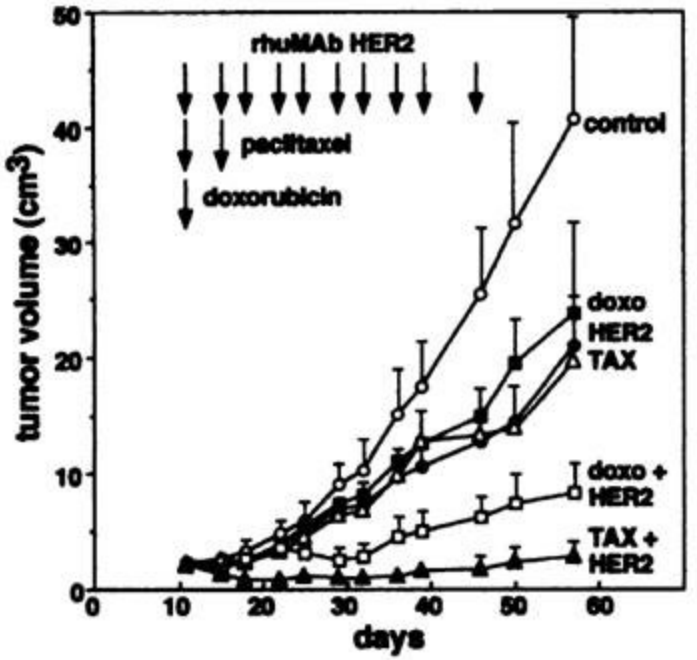
Research Proof-of-Concept (POC)

不只是用動物做實驗

Research POC 研究觀念驗證

- 符合產業界評估觀點的實驗設計
- 先找出competitor（競爭藥物）
- Positive Control: Standard of care (SOC)/ Competitor
  - ✓ Optimal dose; effective model
  - ✓ Negative control: vehicle, placebo, etc.
- Relevant disease model
  - ✓ 已有成功預測臨床經驗
  - ✓ 已上市藥物的實驗設計
  - ✓ 法規單位公告之研發指引
  - ✓ 具公信力的文獻
- 模擬臨床使用情境

Herceptin + chemo



Cancer Research 58 (1998) 2825-2831

以開發治療HCC的藥物為例

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Hepatocellular Carcinoma

PRINCIPLES OF SYSTEMIC THERAPY

- First-line systemic therapy
  - Preferred
    - Sorafenib (Child-Pugh Class A [category 1] or B7)[a,b,1,2]
    - Lenvatinib (Child-Pugh Class A only)[3]
  - Other Recommended
    - Systemic Chemotherapy (category 2B)[c]

- Subsequent-line therapy if disease progression:
  - Regorafenib (Child-Pugh Class A only) (category 1)[d,4]
  - Cabozantinib (Child- Pugh Class A only) (category 1)[d,5]
  - Ramucirumab (AFP ≥ 400 ng/mL only) (category 1)[d,6]
  - Nivolumab (Child-Pugh Class A or B7)[7]
  - Sorafenib (Child-Pugh Class A or B7)[a,b] (after first-line lenvatinib[e])
  - Pembrolizumab (Child-Pugh Class A only)[8]

TPP參考基準 --競爭藥物仿單

注意
✓ 最新版本
✓ 隨時更新

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information need
NEXAVAR safely and effectively.
See full prescribing information for NEXAVAR.

NEXAVAR (sorafenib) tablets, for oral use
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Cardiovascular Events (5.1)	12/2018
Dosage and Administration, Dose Modifications for Adverse Reactions (2.2)	12/2018

---------- INDICATIONS AND USAGE----------

NEXAVAR is a kinase inhibitor indicated for the treatment of

- Unresectable hepatocellular carcinoma (1.1)
- Advanced renal cell carcinoma (1.2)
- Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment (1.3)

----------DOSAGE AND ADMINISTRATION----------

- 400 mg (2 tablets) orally twice daily without food. (2.1)
- Treatment interruption and/or dose reduction may be needed to manage adverse reactions. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

200 mg Tablets (3)

---------- CONTRAINDICATIONS ----------

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR. (4)
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Cardiovascular Events: Consider temporary or permanent discontinuation of NEXAVAR. (2.2, 5.1)
- Bleeding: Discontinue NEXAVAR if needed. (5.2)
- Hypertension: Monitor blood pressure weekly during the first 6 weeks and periodically thereafter. (5.3)
- Dermatologic Toxicities: Interrupt and/or decrease dose. Discontinue for severe or persistent reactions, or if Stevens-Johnson syndrome and toxic epidermal necrolysis is suspected. (5.4)
- Gastrointestinal Perforation: Discontinue NEXAVAR. (5.5)
- QT Prolongation: Monitor electrocardiograms and electrolytes in patients at increased risk for ventricular arrhythmias. (5.9, 12.2)
- Drug-Induced Liver Injury: Monitor liver function tests regularly; discontinue for unexplained transaminase elevations. (5.10)
- Embryo-Fetal Toxicity: NEXAVAR may cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.11, 8.1, 8.3)
- Impairment of TSH suppression in DTC: Monitor TSH monthly and adjust thyroid replacement therapy in patients with thyroid cancer. (5.12)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥20%) for NEXAVAR are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS----------

- Avoid strong CYP3A4 inducers. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise women not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status prior to initiation of NEXAVAR. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 12/2018

撰寫TPP --參考競爭藥物仿單

Target Product Profile for Developing an Anti-HCC Drug

Therapeutics Area	Oncology		
Efficacy (pre-clinical)	In the PLC/PRF/5 HCC xenograft model, 10		
Target population	Patients who have unresectable hepatocellular carcinoma or advanced renal cell carcinoma		
Dosage/form / Route of Administration	200 mg/tablet/p.o.		
Dose (frequency)	400 mg (2 tablets) orally twice daily without food		
Formulation and Dosing Regimen	Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.		
Durability (API Half Life T1/2)	The mean elimination half-life of sorafenib is approximately 25–48 hours		
Clinical Efficacy	1. SHARP Trial:		

General consideration

TPP Example 1

- 開發非複雜惡性瘧疾（Uncomplicated Falciparum Malaria）藥物

1. 口服劑量（最好一天一次，但一天不超過三次）
2. 低成本（每個完整療程約1美元）
3. 對具抗藥性瘧原蟲（如對chloroquine或sulfadoxine-pyrimethamine治療已產生抗藥性之瘧原蟲）有效
4. 作用快速，三天內治癒
5. 能與其他藥物合併使用的可能性
6. 具有兒童使用劑型
7. 在熱帶氣候下藥品可保持穩定
8. IP：需要能自由實施（FTO）的專利，最好能有物質組成專利保護

TPP Example 2

- 開發治療原蟲及寄生蟲疾病藥品之hit到lead階段TPP

1. 抗原蟲藥物篩選的體外活性試驗Plamodium falciparum：IC50<0.2μg/mL Trypansoma cruzi：IC50<1.0μg/mL
2. 抗寄生蟲藥物篩選Schistosoma mansoni：100%抑制成蟲的活動力，IC50<2μg/mL, Onochocercalienalis, O. ochengi, 或O. volvulus：在1.25x10-5M或10μg/mL的濃度下能100%抑制微絲蟲的移動力
3. 建立分子標的的選擇性，或在寄生蟲和宿主酵素間的敏感性差異應達10倍以上。
4. 以口服或腹腔注射方式投與高達100 mg/kg之藥品給未受感染之小鼠進行預毒性測試（Pre-toxicity screen）。
5. 以小鼠或倉鼠進行活性測試：在4x50mg/kg劑量下，能顯著降低血中寄生蟲濃度且/或延長壽命，不論是以口服或腹腔注射方式投與且皆無顯著的毒性。
6. 至少在兩個物種（包含人類），確認藥品在肝臟微粒體的代謝穩定性。
7. hERG實驗結合濃度>10μM。
8. 對細胞酵素Cytochrome P450抑制性低。
9. IP：應該具新穎性且可申請物質組成專利。

精簡、正確、可量化

TPP Example 3

- 膠質母細胞瘤藥品臨床開發

1. 使用族群：尋求被核准於單獨使用，或與bevacizumab併用，治療於接受放射線與temozolomide合併治療後復發的多型性膠質母細胞瘤之病患。
2. 療效：無惡化存活期（PFS）的中位數大於6.3個月（單獨使用bevacizumab則為4.2個月），合併治療下整體存活期的中位數大於9個月。
3. 安全性：大部分患者有三到四級嗜中性白血球低下（neutropenia）情況，這部分可藉補充生長因子來克服。發生三到四級神經病變（neuropathy）的病患小於10%。其他毒性問題均為可控管、可預測及可回復的。
4. 劑量：每三周一次療程靜脈注射120 mg/m2藥品，到疾病復發為止或共六個療程。
5. IP：尋求與bevacizumab併用具新穎性之專利保護。
6. 穩定的供應鏈，每小瓶的商品成本小於50美元。

視產品研發階段考量不同的重點

學界撰寫TPP尚待改進之處

- 適應症未聚焦；未設定最具競爭利基之優先開發的適應症、目標病人族群、競爭藥物, etc.
- 未更新動態
- 只有現況摘要，未設定產品目標特性
- 未量化，缺乏go/no-go criteria概念
- 缺乏跨領域評估思考
- 商業面考量不足，鮮少思考商業營運模式

TPP --References

- Daria, Mochly-Rosen and Kevin Grimes, A Practical Guide to Drug Development in Academia, The SPARK Approach, p. 20-23, Springer, 2014.
- Guidance for Industry and Review Staff, Target Product Profile — A Strategic Development Process Tool. Draft guidance, CDER, FDA, 2007.
- 藥物開發評估利器—目標產品概況簡介；2015年12月科學月刊／科技報導
- Lei Chuang's presentation at 2015 Si²C-SPARK Symposium
- Dr. Chia-Hsin Yeh's presentation for SPARKees, since 2015
- Dr. Herng-Der Chern's presentation at SPARK TW, Sep. 19, 2018
- Dr. M. Sherry Ku's presentation at TRPMA, Jul. 26, 2018

歡迎指正

THANKS FOR YOUR ATTENTION