出國報告（出國類別：國際會議）

參加 2013 年第 73 屆世界藥學會報告

（73th International Congress of FIP）

服務機關　：衛生福利部食品藥物管理署

姓名職稱　：王力以技士

派赴國家　：愛爾蘭

出國期間　：102 年 8 月 30 日至 102 年 9 月 7 日

報告日期　：102 年 12 月 06 日

摘　　要

每年，世界藥學會(Internatio nal Pharmaceutical Federation) 都會訂定一個主題來舉辦藥學和製藥科學的大會，並輪流由世界各個國家城市舉辦，今年是由愛爾蘭為其主辦國家，大會日期從 8 月 31 日至 9 月 5 日在首都都柏林會議中心舉辦。往年該會都以專注於全球製藥實踐和製藥科學為主，並依其大會主題以辦理各種相關之座談會、研討會、討論會及海報展覽。

今年 2013 年的主題是考量面對未來的病患，不再只是需要單純的照護，而是因應患者和醫療保健系統因受到科學、技術和通信的不斷發展下，而產生醫療系統將面對一個動態的、連續的且更複雜的病患綜合照護。因此藉由本次會議討論藥師面對此更具挑戰性的環境中，如何提升成為一個病人照護更重要的核心的功能。

本署管制藥品製藥工廠於本次以「Process Improvement of Ampoule Leak Testing」為標題發表一篇海報論文，主要是展示製藥工廠於注射劑之安瓿熔封後，突破以傳統色水方式來檢測洩漏情形之不足，改以利用加壓真氣來進行洩漏檢查之成果，將其成果與各國與會者分享、研討及交換心得，並希望能在會議中，瞭解及蒐集全球藥學最新的資訊與發展趨勢，以提升知能及競爭力。

DUBLIN 2013
FIP WORLD CONGRESS
31 August - 5 September

參加 2013 年第 73 屆世界藥學會報告

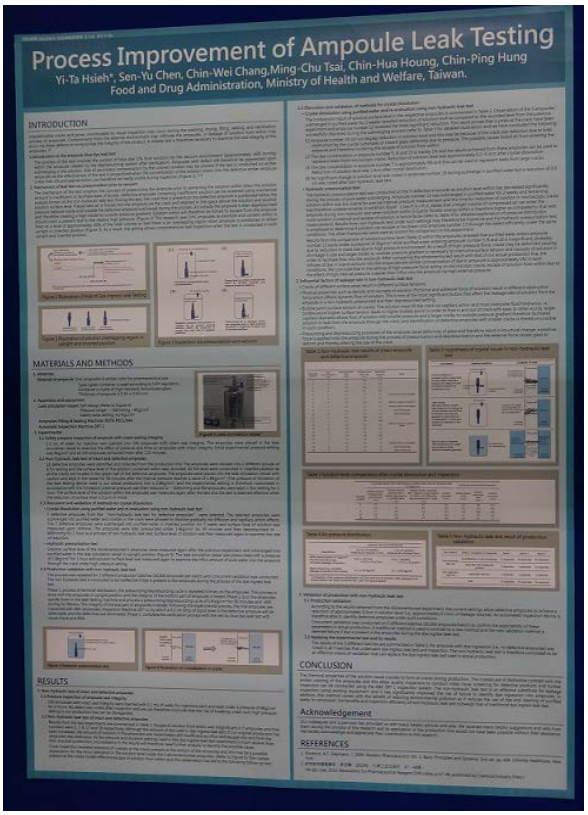
目　　次

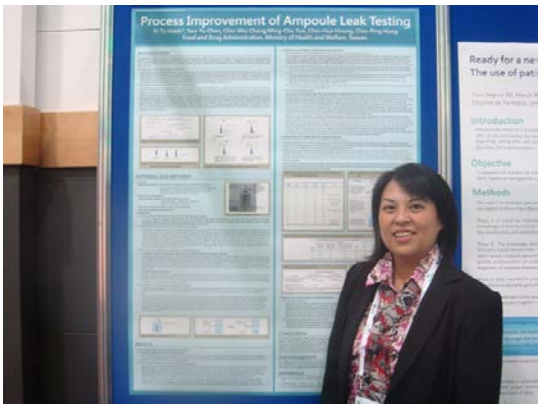
第一章 目的

本次參加的世界藥學會 (International Pharmaceutical Federation, FIP) 是於 1912 年成立於荷蘭，現今會址在荷蘭海牙，目前擁有 127 個會員國；包含約 200 萬名各國藥師或藥學相關學者、國際護理學會（ICN）及世界醫師協會（WMA），所合組成的國際衛生專業人員聯盟（WHPA），是 WHO 下最具規模之衛生相關組織非政府組織（NGO）。該學會會務主要分為兩大組別：藥學科學組(Board of Pharmaceutical Science)與藥學執業組(Board of Pharmaceutical Practice)，然後由這兩大組別再各自細分諸多小組。目前在台灣的會員組織有台灣藥學會、台灣臨床藥學會。

每年 FIP 均會訂定主題並召開年會，且輪流由世界各國擇一城市舉辦，今年（2013）年會則選定於愛爾蘭都柏林的會議中心(Convention Centre Dublin, CCD)舉辦，希望來自全球各領域之藥師（臨床、社區）、藥學界有貢獻之藥師及其他與藥學相關的從業人員皆能參加與會，並藉由海報展示、專題演講等方式來作為彼此間研究心得的交換及相關議題之探討，進而瞭解世界各國藥學各領域的發展之動向。

本署管制藥品製藥工廠於今年亦積極參與並通過大會海報「工業製藥組」項中的審核，以「Process Improvement of Ampoule Leak Testing」為標題發表一篇海報論文，主要是展示製藥工廠於注射劑之安瓿熔封後，突破以傳統色水方式來檢測洩漏情形之不足，改以利用加壓真氣來進行洩漏檢查之成果，因此派員參加，並希望除於會場中海報展示本署管制藥品製藥工廠研發成果外，參與同仁可從各項研討會中獲得全球藥學最新的資訊與發展趨勢，提供製藥工廠製造及管理管制藥品改進參考，提升製藥工廠製藥水準，並促進我國專業國民外交之實務、視野與願景之提升。





第二章 會議過程

一、 行程概要：

本次出國參加由台灣藥學會、台灣年輕藥師學會及社團法人台灣臨床藥學會三會聯合協辦之會議團出席 2013 世界藥學會年會，其行程概要如下：

行 程 表			
會議名稱	第73屆 世界藥學會年度會議	會議地點	愛爾蘭都柏林

天數	日 期	行 程 內 容	備 考
1	08 月 30 日 （星期五）	從臺灣桃園國際機場搭乘08月30日上午9:00長榮航空班機飛行約3.5小時，於12:40抵達曼谷機場待轉機飛往倫敦。 曼谷機場當地時間13:20(-1hr)搭乘長榮航空班機飛行約11小時抵達英國倫敦機場。	
2	08 月 31 日 （星期六）	隨團參訪考察+搭乘英國航空班機飛往愛爾蘭都柏林。 愛爾蘭第 73 屆世界藥學會會前 meeting	
3	09 月 01 日 （星期日）	前往愛爾蘭參加第 73 屆世界藥學會會場 15:00-17:00 Opening Ceremony 。 17:00-19:00 Opening Exhibition and FIP & Taiwan /FAPA Reception。	
4	09 月 02 日 （星期一）	愛爾蘭-全日參加大會所安排之會議(09:00-17:00) 第一梯次 Poster 張貼 19:30-21:00 Welcome Reception	
5	09 月 03 日 （星期二）	愛爾蘭-全日參加大會所安排之會議(09:00-17:00) 第二梯次 Poster 張貼 06:45-08:00 FIP Fun Run 19:00 Young Pharmacists Group:YPG Evening	
6	09 月 04 日 （星期三）	愛爾蘭-全日參加大會所安排之會議(09:00-17:00) 第三梯次 Poster 張貼 20:00-24:00 Closing Dinner	
7	09 月 05 日 （星期四）	愛爾蘭-全日參加大會所安排之會議(09:00-17:00)	
8	09 月 06 日 （星期五）	愛爾蘭都柏林－倫敦+隨團參訪考察	
9	09 月 7 日 （星期六）	倫敦－曼谷－台北	

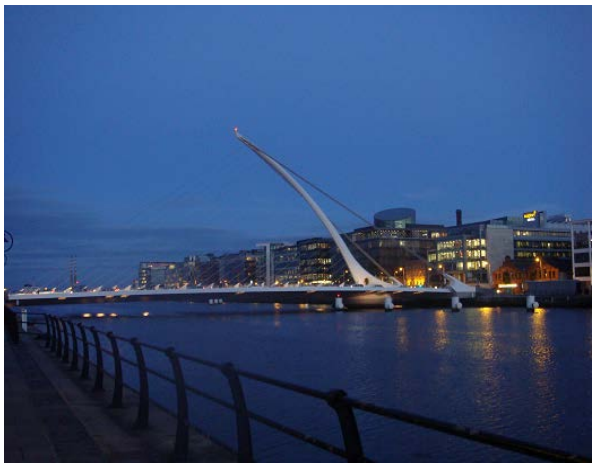
二、 會場過程：

(一) 報到：

本年度國際藥學聯合總會(FIP)於愛爾蘭都柏林召開「第73屆世界藥學會」，會議日期從8月30日至9月5日，會中全球共有來自106個國家，約2,714人報名參與盛會，其中台灣報名參加者有82人。9月1日開幕式前會議團一行人即前往大會會場，辦理報到手續並領取大會手冊(含參加人員名冊、摘要集、大會議程等)。

(二)　開幕：

2013年73屆世界藥學會年會於9月1日15:00~17:00舉行開幕式。今年主辦之地主國為愛爾蘭(Ireland)，其會議地點位於愛爾蘭首都都柏林利霏河畔（Liffey River)旁的Convention Center Dublin（CCD）會議中心舉辦。



今年是愛爾蘭繼1975年第二次舉辦世界藥學大會，由於愛爾蘭在近幾年藥學立法的改變，促使愛爾蘭藥師的角色呈現不斷的蛻變，除了可發揮藥師藥學專業外，亦是成為擔負起照顧民眾健康之重要成員之一。在開幕典禮中愛爾蘭的衛生部部長James Reilly TD、愛爾蘭藥學會新任會長Eoghan Hanly皆出席參與。當時主辦的愛爾蘭衛生部部長在開幕詞中便提到了患者和醫療保健系統的日益複雜，其複雜包括了壽命的增加及更好的醫療技術，這些發展將對醫療保健系統方面的資金產生更大的挑戰，因此如何要求更好和更負責任地使用有限的資源。因此鼓勵健康的生活方式、預防疾病及促進更負責任地使用藥物是現行藥師的主要任務。

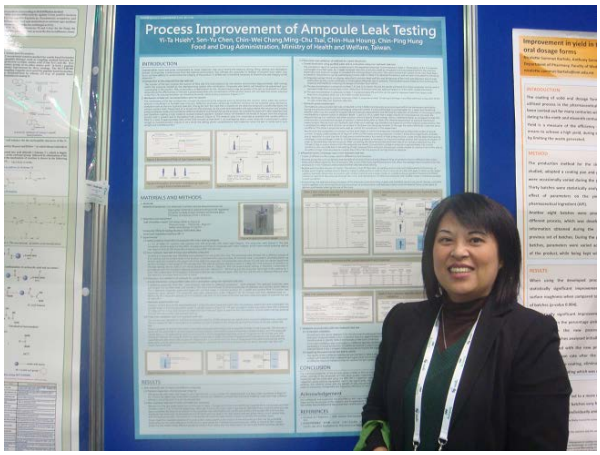
另FIP主席Michel Buchmann也表示，在全球我們有300萬的藥師為藥學及科學努力，今年FIP以「關照複雜性病人(Towards a Future Vision for Complex Patients)」為主題，表明當醫療發揮作用，而促使人們活得更久，相對地疾病也隨之複雜化，許多的問題因應而出，不管在愛爾蘭還是其他國家，在有限的經濟資源下，對於複雜性病人的藥事照護及提供更好更創新藥物都有著憧憬，因此，今年度匯集大家於此，藉由各國的經驗分享，讓各國的藥師互相認識，並同時在錯誤中學習成長。

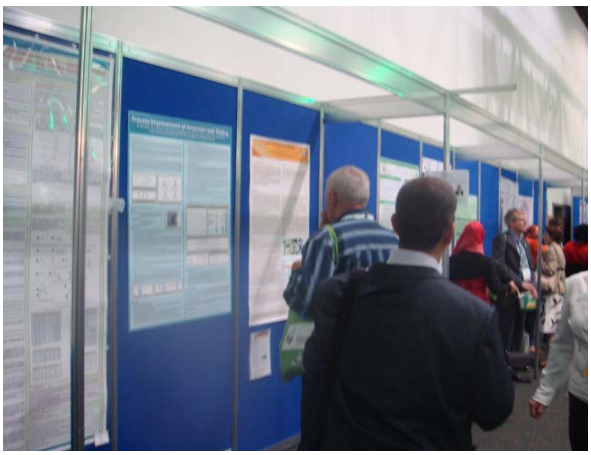
(三)　台灣迎賓會：

在大會開幕典禮精彩的演講與節目之後，Taiwan/FAPA迎賓宴緊接登場，由臺灣臨床藥學會、台灣藥學會、台灣年輕藥師協會及亞洲藥學會所聯合舉辦。台灣迎賓宴自2004年首度舉行至今已邁入第10個年度，2009年起更與亞洲藥學會合作擴大規模，更名為Taiwan/FAPA迎賓宴，到現在已成為FIP年會的一項傳統，讓來自世界各地的友人再聚首，共同歡慶這一年一度大會。當天出席人數超過400人，來自美國、澳洲、馬來西亞…等30多個國家的友人皆熱情參與；而我們的駐愛爾蘭代表處曾大使厚仁也偕同代表處人員撥冗出席給予支持和鼓勵。

(四)　海報展示：

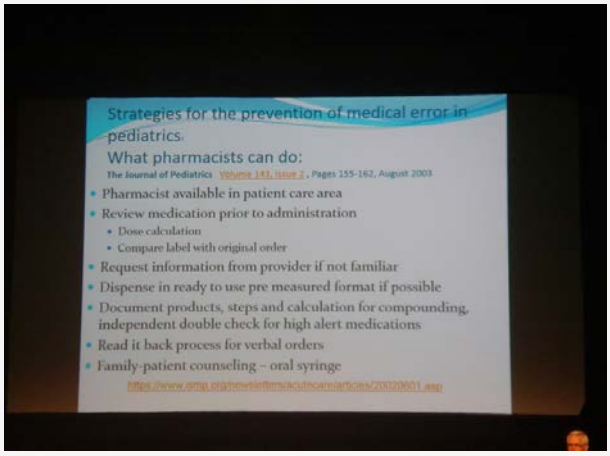
今年FIP核可張貼海報多達683件，因此主辦國依參展海報內容予以分成22項組別，並於會議期間以三個梯次分別張貼展示（第一梯次展示期間為9月2日至3日、第二梯次為9月3日至4日、第三梯次為9月4日至5日），本署管制藥品製藥工廠以「Process Improvement of Ampoule Leak Testing」為題發表一篇海報論文，並與參加與會者分享經驗及相互交流。



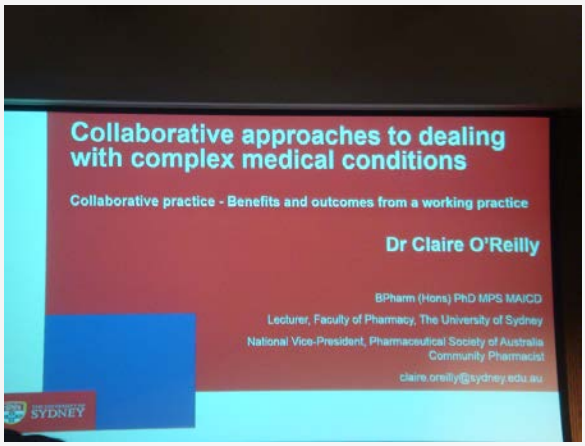


(五)　專題演講：

今年 FIP 以「關照複雜性病人(Towards a Future Vision for Complex Patients)」為主題，主要是因應未來在科學、技術和通信之不斷發展的環境下，醫療也隨在此一個動態的、連續的變化中促使病患將因這些醫療的提升，而使民眾增加壽命的延長；當壽命延長將導致病人走向更複雜性的綜合照護，藥師除須了解身為藥師對於這樣複雜的病人該如何照護及對於自身的角色將會是越來越重要外，更應了解影響複雜性的因素[如：生物面(強調系統生物學的發展現狀)，醫療面（人口統計、遺傳、吸煙、酗酒、飲食和多種疾病)，社會經濟面（可用資源及素養）和文化面（信仰、傳統及宗教）等]，才能知道如何面對這樣的未來，並提升成為一個病患照護更重要的核心的功能。因此，為提供與會藥師能廣泛的學習及有所成長，大會針對本次主題可能牽涉的所有觀點安排了相關的演講作為本次大會主要的課程，另外大會舉辦多場的演講課程：包括以為什麼患者是複雜性？什麼是複雜性患者的需求？我們正在做什麼以滿足複雜性患者的需求？治療複雜患者的新興策略是什麼？藥學教育現狀建立管理複雜的患者的途徑及培訓複雜性未開發的領域等六大議題，分別邀請該領域的專家進行專題演講並分享其經驗。




Meeting the Needs of Complex Patients
Session C1: Best Practice in Integrating Drug Therapy and Patient Care
Safety and efficiency evidence, for a collaborative pharmaceutical service program, as is currently implemented in Swiss nursing homes
The 3rd of September 2013


Collaborative approaches to dealing with complex medical conditions
Collaborative practice - Benefits and outcomes from a working practice
Dr Claire O'Reilly
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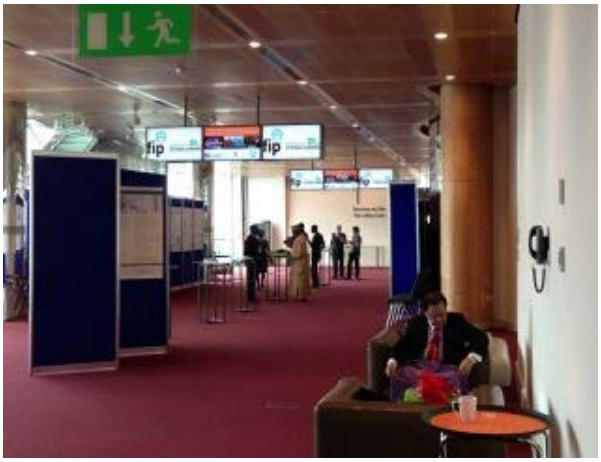
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第三章　心得及建議

今年大會對於六大議題中安排非常多相關的專題演講供與會者選擇，因此就時間安排上僅能選擇部分課程前往聆聽。此次課程中對於大會主題中什麼是複雜性患者的需求？我們正在做什麼以滿足複雜性患者的需求？治療複雜患者的新興策略是什麼？等相關課程之專題演講大多以社區藥師的角色作為探討，其中一堂「Best practice in integrating drug therapy and patient care」，講者在演講中提到隨著時代的演變，藥局從純粹給藥到諮詢服務再發展至藥事照護，藥局的經營模式不斷的在改變；社區藥局藥師在經營藥局的過程當中，除提供諮詢的功能外，應是展現其專業的最佳時機。身為社區藥局藥師，應了解病人的需求才能優化治療的效果，然而需了解哪些需求呢？主要有 3 大部分，首先應知道病人服用哪些處方藥：也就是要收集患者基本資料與疾病和用藥的相關資訊，以作為判斷藥物治療適當性之依據，另再根據這些資料來判斷病人藥物治療是否有滿足病患之需求；其次是認識病人：社區藥局藥師與病人之間應建立一長期用藥安全顧問之外的情誼，使病人除對藥師所提供的藥事服務或店售商品感到滿意外，更應該取得病人對社區藥局藥師的信賴及信任感，方能真正為病人健康做守護；最後應能取得病人臨床檢驗報告：了解病人在服用藥物後，血液中各種檢驗數值及藥物濃度之變化，方可適時知道病人服藥正確性，雖然在現今的醫療體系中多半仍以醫師為主，但講者認為不論是醫師或護理人員對於藥物的主要藥理機轉之認知上，絕對不及藥師，因此藥師應站在一個專業角度去協助病人做更正確的用藥，這是身為藥師應積極去努力的目標。

另一堂課是針對以兒童用藥方面進行探討，講者認為兒童是處於在生長的階段，他們的肝腎功能、中樞神經系統和內分泌系統都還沒有發育健全，因此兒童體內所呈現的藥動學與藥效學與成人有相當大的差別，也就是說對於許多藥物的代謝、排泄和耐受力較成人差，因而產生藥物不良反應的發生率自然高。

然而兒童在用藥方面應使用兒科的專用配方，但事實上目前大部分醫事人員對於兒童藥物的使用，通常還是採取以成人服用的錠劑、膠囊劑的減量方式來供作兒童的使用，但兒童用藥劑量與成人劑量並不相同，且劑量不易計算，因此不論是社區藥劑師或臨床藥劑師對於兒童的用藥應正視為一複雜性的用藥照護，並利用專業知識積極宣導兒童用藥正確認知供家長知悉，方可有效促使衛生主管機關重視兒童用藥政策擬定。

還有一課堂主題為「Collaborative approaches to dealing with complex medical conditions」，本課程主要探討因醫療環境變遷，隨之促使醫療技術的提高，長壽的患者亦日趨增加，這些長壽者伴隨著這種增長而衍生更多種慢性疾病的發生，然而對於這樣的患者的治療勢必更加複雜，身為醫療保健專業人員之間的相互協作更顯現重要，以確保患者不論在醫療、照護、藥物、及提高患者的預後和提高患者自己的健康知識的福祉都能有效地提升。因此藉由本次會議由各國將曾相互協作實踐的幾種有效情況進行分享，也重新定位未來藥師應花費較多的時間在與病人、醫生及護士溝通、以發揮專業知識提高專業形象。

歷經幾日來大會所安排之課程後發現，由於各國執行醫藥分類強制性不同，而使得原僅著重於配藥功能及藥物品質的傳統藥師角色，轉換成著重在病患用藥結果為中的角色，依據世界衛生組織與世界藥學會共同制定的藥事服務核心功能中提到，藥師應提供一定品質之藥品、藥物資訊、病患用藥諮詢及監測追蹤藥品的使用結果。由此可知在醫藥領域中，各國藥師地位已不斷在提升中，其中印象最深刻是有講者以加拿大藥師為例，說明加拿大的藥師幾乎是「病患的代言人」，藥師發揮其專業性，幫助醫師與病患做更有效的溝通，且被醫師與病患認同，因此，在加拿大若藥師提供具服務性的建議文件給醫師，政府就會支付費用給藥師，我覺得這是對一位藥師專業度的肯定，但反觀國內在醫藥領域中仍以醫師為主，國家培育出的藥師、護理師等人才，仍無法依其專長提供建議並偕同照護病患，此現象也容易造成我國醫療資源的極大浪費，因此，面臨我國健保虧損的漏洞，我個人認為若要解決此一問題應善用藥師專長，使民眾能真正依其病症正確用藥，不但可避免民眾錯誤用藥造成身體功能損傷，亦可藉由藥師傳達讓民眾更重視自身健康且建立良好的健康促進之概念，以此降低疾病發生進而節省醫療資源，轉而將此資源用在真正需要的民眾身上，以達全民健康之目標。爰此，建議相關機關應積極研擬出如何讓醫療機構之專業人員能真正發揮--人盡其才物盡其用，方能面對未來更複雜、更有限的醫療資源下，提供最好的醫療品質，以達到並創造人民及政府雙贏的局面。

除了課程外，大會於海報展覽區也設置許多廠商駐點，其中有許多駐點廠商多因應未來社區藥師已不再以調配藥物為主要工作，而研發一些自動撿藥機器設備或配藥包裝外加註藥品仿單或病患服藥資料之 QR code，以節省社區藥師調配藥物的時間，讓藥師能有較多的時間在與病患、醫生及

護士進行溝通，以達到利用最低的醫療資源來達到最佳的醫療照護，如此才能提升藥師的專業成效。

回國後，細細思量本次對於世界藥學會所分享的課程中，讓我瞭解到在面對未來複雜性病患中，勢必也包括使用管制藥品的病患，身為藥廠除須符合製藥法規外，是否應思考如何更順應時勢及病患所需，除提供更佳藥物品質外，亦應考慮使用端之方便性，雖然國內目前對於管制藥品的處方籤尚未釋放至社區藥局，但據了解新北市衛生局已開始研擬釋放至社區藥局之可行性，因此身為藥廠人員應考量，對於未來管制藥品除應提升產品品質外，是否更應提供臨床藥局藥師及社區藥局藥師更省時之調劑作業，例如：依健保給付天數制定每盒裝藥錠之數量，每次提供一盒包裝，則不論是利用人工或撿盒機作業都可節省許多工時，也可讓病患了解服藥情形；另本廠亦可考慮未來智慧型手機之普及性，對於產品仿單資訊是否可透過包裝外盒 QR code，來提供更多相關訊息，以上是本次出國個人心得及建議。

附件：海報論文

Process Improvement of Ampoule Leak Testing

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INTRODUCTION

Unpredictable cracks and pores unnoticeable by visual inspection may occur during the washing, drying, filling, sealing, and sterilization process of ampoules. Contaminants from the external environment may infiltrate the ampoules, or leakage of solution from within may occur via these defects to compromise the integrity of the product. A reliable test is therefore necessary to examine the seal integrity of the ampoules. [2]

1.Introduction to the ampoule blue dye leak test

The process of the test involves the suction of blue dye (1% blue solution) by the vacuum environment (approximately -600 mmHg) within the ampoule created by the depressurizing system after sterilization. Ampoules with defect will therefore be pigmented upon submerging in the solution. Risk of secondary contamination by the colored solution may be present if the test is conducted on amber ampoules as the effectiveness of the test is jeopardized when the concentration of the solution drawn into the defective amber ampoule is less than 2% and pigmentation can therefore be hardly visible during inspection (Figure 1). [1,2]

2. Mechanism of leak test via pressurization prior to vacuum

The mechanism of the test employs the concept of pressurizing the ampoule prior to extracting the solution within when the solution amount is insufficient to facilitate ease of access. Defective ampoules containing insufficient solution can be screened using mechanical analysis known as the non-hydraulic leak test. During the test, the crack that is present on the defective ampoule is positioned below the solution surface level. Pressurized air is forced into the ampoule via the crack and retained in the space above the solution and positive pressure balance inside and outside the defective ampoule is achieved during the process. Air outside the ampoule is then depressurized and therefore creating a high inside-to-outside pressure gradient. Solution within will therefore be forced to escape from the ampoule should crack is present due to the relative high pressure. (Figure 2) This research uses 1mL ampoules as example and content within is filled to a level of approximately 60% of the total volume so that there is an overlapping region when ampoule is positioned in either upright or inverted position (Figure 3). As a result, the setting allows comprehensive leak inspection when the test is conducted in both upright and inverted position.

Figure 1 Illustration of Risk of Dye Ingress Leak Testing

Figure 3 Illustration of solution overlapping region in upright and inverted position

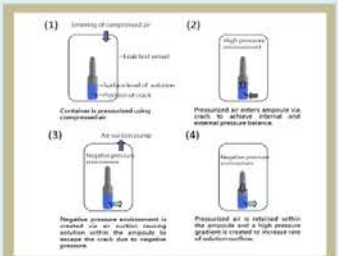


Figure 2 Inspection via pressurization and vacuum

MATERIALS AND METHODS

1. Materials

Material of ampoule: 1mL ampoules in amber color for pharmaceutical use
Type I glass container is used according to USP regulation.
Container is made of high resistant, borosilicate glass.
Thickness of ampoule is 0.45 ± 0.03 mm.

2. Apparatus and equipment

Leak simulation vessel: Self-design (Refer to Figure 4)
Pressure range: - 760mmHg ~ 4Kg/cm²
Safety valve setting: 4.2 Kg/cm²

Ampoules Filling & Sealing Machine: ROTA R921/MA
Automatic Inspection Machine 287-1

3. Experimental

3.1 Safety pressure inspection of ampoule with intact sealing integrity

1.1 mL of water for injection was injected into 100 ampoules with intact seal integrity. The ampoules were placed in the leak simulation vessel to examine the effect of pressure and time on ampoules with intact integrity. Initial experimental pressure setting was 4kg/cm² and all 100 ampoules remained intact after 120 minutes.

Figure 4 Leak simulation vessel

3.2 Non-hydraulic leak test of intact and defective ampoules

16 defective ampoules were identified and collected from the production line. The ampoules were divided into 2 different groups of 8 for testing and the surface level of the solution contained within was recorded. All the tests were conducted in inverted position as all the cracks are located in the upper half of the defective ampoules. The ampoules were placed into the leak simulation vessel with caution and kept in the vessel for 30 minutes after the internal pressure reaches a value of 1.8Kg/cm². (The pressure of limitation of the leak testing device used in our actual production line is 1.8Kg/cm², and the experimental setting is therefore customized in accordance with this limitation) Internal pressure was then reduced to - 600mmHg and the ampoules were kept in this setting for 1 hour. The surface level of the solution within the ampoules was measured again after the test and the test is deemed effective when the reduction of surface level is 0.2cm or more

3.3 Discussion and validation of methods for crystal dissolution

• Crystal dissolution using purified water and re-evaluation using non-hydraulic leak test

5 defective ampoules from the "non-hydraulic leak test for defective ampoules" were selected. The selected ampoules were submerged into purified water and crystals in the crack were allowed to dissolve gradually via diffusion and capillary action effects. The 5 defective ampoules were submerged into purified water in inverted position for 2 weeks and surface level of solution was measured upon removal. The ampoules were later pressurized under 1.8kg/cm² for 30 minutes and then depressurized to - 600mmHg for 1 hour as a process of non-hydraulic leak test. Surface level of solution was then measured again to examine the rate of reduction.

• Hydraulic pressurization test

Solution surface level of the aforementioned 5 ampoules were measured again after the previous experiment and submerged into purified water in the leak simulation vessel in upright position (Figure 5). The leak simulation vessel was pressurized with a pressure of 1.8kg/cm² for 1 hour and solution surface level was measured again to examine the influx amount of pure water into the ampoule through the crack under high pressure setting.

3.4 Production validation with non-hydraulic leak test

The process was repeated for 3 different production batches (30,000 ampoules per batch) and concurrent validation was conducted. The non-hydraulic test is concluded to be ineffective if dye is present in the ampoules during the process of the dye ingress leak test.

Phase 1, process of terminal sterilization, the pressurizing/depressurizing cycle is repeated 4 times on the ampoules. This process is done with the ampoules in upright position and the integrity of the bottom part of ampoules is tested. Phase 2, turn the ampoules upside down in the leak-testing machine and process a pressurizing/depressurizing cycle of 1.8 kg/cm² for 60 minutes and -600 mmHg for 90mins. The integrity of the top part of ampoules is tested. Following the experimental process, the trial ampoules are inspected with AIM (Automatic Inspection Machine 287-1), by which a 0.2 cm drop of liquid level in the defective ampoule will be detectable, and the defectives are eliminated. Phase 3, complete the verification process with the rest by blue dye leak test with visual check and AIM.

Figure 5 Hydraulic pressurization test

Figure 6 Illustration of crystallization in cracks

RESULTS

1. Non-hydraulic test of intact and defective ampoules

1.1 Pressure inspection of ampoule seal integrity

100 ampoules with intact seal integrity were injected with 1.1 mL of water for injections each and kept under a pressure of 4Kg/cm² for 2 hours. No defect was noted after inspection and we can therefore conclude that the risk of breaking under such high pressure setting in our production line can be disregarded.

1.2 Non-hydraulic leak test of intact and defective ampoules

Results from the two experiments are summarized in Table 1. Escape of solution from within was insignificant in 5 ampoules and their numbers were 5, 7, 8, 13 and 18 respectively. Although the amount of dye used in dye ingress leak test of our original production has been increased, the amount of solution in the ampoules was nevertheless still insufficient as influx and escape into and from the ampoules was strenuous. As the pressure and duration settings used in this dye ingress leak test experiment is much severer than that of actual production, inconsistency in the results will therefore need further analysis to identify the possible cause.

Close inspection revealed presence of crystals at the cracks present at the bottom of the ampoules and this may be a possible explanation for the minor alteration in the solution level inside the 5 aforementioned ampoules. (Refer to Figure 6) The crystals present at the cracks hinder effective escape of solution from within and this observation has led to the following follow-up test.

1.3 Discussion and validation of methods for crystal dissolution

• Crystal dissolution using purified water and re-evaluation using non-hydraulic leak test

The comparison result of solution surface level in the respective ampoules is summarized in Table 2. Observation of the 5 ampoules submerged in purified water for 2 weeks revealed reduction of solution level as compared to the recorded level from the previous experiment and ampoule number 13 revealed the most significant reduction. This result proves that crystals at the crack have been successfully dissolved during the submerging process (refer to Table 3 for detailed illustration) and we have concluded the following:

(1) Ampoule number 18 did not display reduction in solution level and this may be because of the crack size reduction due to total obstruction by the crystal substrates or inward glass deformity due to pressure. The possible causes forbid air from entering the ampoule and therefore hindering the escape of solution from within.

(2) The dye concentration in ampoule number 5, 8, and 13 is merely 1% and the results achieved from these ampoules can be used to represent leaks from microscopic cracks. Reduction of solution level was approximately 0.2~0.3cm after crystal dissolution.

(3) The dye concentration in ampoule number 7 is approximately 9% and this can be used to represent leaks from large cracks. Reduction of solution level was 1.4cm after crystal dissolution.

(4) No significant change in solution level was noted in ampoule number 18 during submerge in purified water but a reduction of 0.9 cm was noted after non-hydraulic leak test.

• Hydraulic pressurization test

The hydraulic pressurization test was conducted on the 5 defective ampoules as solution level within has decreased significantly during the process of pure water submerging. Ampoule number 13 was submerged in purified water for 2 weeks and remaining solution within was too scarce for precise internal pressure measurement and the time for reduction of solution in microscopic cracks was therefore undeterminable. In addition, Boyle's law $P_1V_1=P_2V_2$ states that a larger volume of compressed air can enter the ampoule during non-hydraulic test when solution within is scarce. Kinetic energy within is therefore higher as compared to that with more solution contained and escape of solution is hence facile (refer to Table 4 for detailed explanation of pressure distribution measurement). Results from non-hydraulic test under such settings may therefore be imprecise and the hydraulic pressurization test is employed to determine if solution can escape or be drawn into ampoule number 13 through the defect efficiently under the same conditions. The other 4 ampoules were used as control for comparison in this experiment.

Results from the comparison of solution surface level (Table 2) within the ampoules revealed that purified water enters ampoule number 13 easily under a pressure of 2kg/cm² while purified water entering ampoule number 5, 8 and 18 is insignificant, probably due to reduction in crack size due to high pressure environment. As a result of high-pressure force, cracks may be deformed causing shrinkage in size and larger inside-to-outside pressure gradient is necessary to overcome surface tension and viscosity of solution in order to facilitate flow into the ampoule. After comparing the aforementioned result with that of our actual production line, the influxes of dye in scarce amount into the ampoules are similar (concentration of dye in ampoule is approximately 1%) in both conditions. We conclude that in the setting of high-pressure force acting on microscopic cracks, escape of solution from within due to the effect of high internal pressure is easier than influx into the ampoule via high external pressure.

2. Influential factors of leakage rate in non-hydraulic leak test

• Cracks of different surface areas result in different surface tensions.

• Physical properties such as density and viscosity of solution (frictional and adhesive force of solution) result in different obstruction force which affects dynamic flow of solution. This is one of the most significant factors that affect the leakage rate of solution from the ampoule in a non-hydraulic pressurized and then depressurized setting.

• Bubble point (surface tension of cracks): The solution must fill the crack via capillary action and must overcome fluid hindrance, i.e., bubble point (higher surface tension leads to higher bubble point) in order to flow in and out of crack with ease. In other words, larger capillary diameter allows flow of solution with smaller pressure and a larger inside-to-outside pressure gradient therefore facilitates solution to leak from the ampoule through the crack; and identification of defective ampoules with smaller cracks is therefore possible in such condition.

• Pressurizing and depressurizing processes of the ampoule cause deformity of glass and therefore result in structural change: a positive force is applied onto the ampoule during the process of pressurization and depressurization and the external force causes glass to deform and thereby altering the size of the crack.

Table 1 Non-hydraulic test results of intact ampoule and defective ampoule

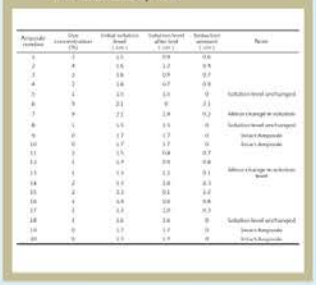


Table 3 Hypothesis of crystal issues in non-hydraulic leak test

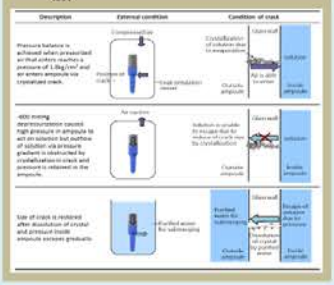


Table 2 Solution level comparisons after crystal dissolution and inspection

Table 4 Air pressure distribution

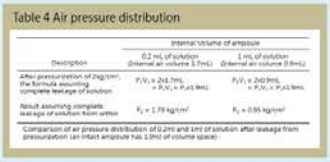
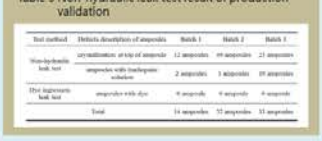


Table 5 Non-hydraulic leak test result of production validation



3. Validation of production with non-hydraulic leak test

3.1 Production validation

According to the results obtained from the aforementioned experiment, the current settings allow defective ampoules to achieve a reduction of approximately 2.0cm in solution level (i.e., approximately 0.13mL of leakage volume). An automated inspection device is therefore able to identify defective ampoules under such conditions.

Concurrent validation was conducted on 3 different batches (30,000 ampoules/batch) to confirm the applicability of these parameters in actual production. A traditional method is used in contrast to a new method and the new validation method is deemed failure if dye is present in the ampoules during the dye ingress leak test.

3.2 Applying the experimental test and its results

The results of the 3 different batches are summarized in Table 5. No ampoule with dye ingression (i.e., no defective ampoules) was noted in all 3 batches that underwent dye ingress leak test and inspection. The non-hydraulic leak test is therefore concluded to be an effective means of validation that can replace the dye ingress leak test used in actual production.

CONCLUSION

The chemical properties of the solution cause crystals to form at cracks during production. The crystals are of distinctive contrast with the amber coloring of the ampoules and this allow quality inspectors to conduct initial visual screening for defective products and further inspection can be conducted using the AIM 287-1 inspection system. The non-hydraulic leak test is an effective substitute for leakage inspection using existing equipment and it has significantly improved the risk of failure to identify dye ingression into ampoules. In addition, this method comes with the benefit of reducing environmental pollution as it reduces the use of dye and cleaning of purified water. In conclusion, the benefits and inspection efficiency of non-hydraulic leak test outweigh that of traditional dye ingress leak test.

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