出國報告（類別：研習）

赴荷蘭動物用藥品檢驗機關
研習動物用疫苗檢驗技術報告

服務機關：行政院農業委員會家畜衛生試驗所
動物用藥品檢定分所
姓名職稱：李淑慧分所長、柯依廷助理研究員
派赴國家：荷蘭
出國期間：**105** 年 **10** 月 **16** 日至 **10** 月 **22** 日
報告日期：**106** 年 **1** 月 **12** 日

赴荷蘭動物用藥品檢驗機關研習動物用疫苗檢驗技術報告

摘要

荷蘭為我國第 2 大動物用疫苗進口國，占動物用疫苗總進口值的 25%，顯見其產品品質已受國內使用者肯定。然而荷蘭之動物用疫苗管理制度及檢驗技術與我國有許多不同之處，例如藥品登記許可後即可進行販售，毋需進行逐批檢驗，而是交由市場機制決定產品優劣，因此動物用藥品主管機關於新藥檢驗登記時之把關以及製藥廠內部品管工作突顯得更為重要。

荷蘭動物疫苗品質把關皆回歸各製藥廠內部品管進行管理，並遵循歐洲藥典規範進行試驗，在動物試驗方面亦遵循實驗動物 3R 原則（減量、取代、精緻化）進行，其取代動物試驗之評估模式有許多值得我國借鏡及學習之處，本次參觀動物用藥廠之管理、動線及就檢驗技術進行討論，有助於提升我國動物用疫苗檢驗之品質與能量。

瓦漢寧恩獸醫生物學研究所為重要動物傳染病的國家實驗室，具有先進之儀器設備、操作高風險病原之實驗室（BSL-3 及 ABSL-4）、以及實驗動物設施，藉由參觀高生物安全等級之實驗室及試驗動物設施，可作為未來動物用藥品檢定分所相關實驗室及動物舍改進參考，以提升檢驗品質。

荷蘭動物用藥品主管機關為 MEB 之動物用藥品管理部門，本次研習與該機關 2 位藥品登記專案主持人就動物用藥管理議題進行討論，與荷方進行登記流程、基因改造疫苗安全性評估流程、以及市售疫苗監測制度等議題進行交流，可作為未來提升動物藥品管理效率提升以及藥品評估流程嚴謹化之重要參考。

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一、緣起及目的

荷蘭為我國第二大動物用疫苗進口國，其動物用疫苗管理制度及檢驗技術與我國有許多不同之處，本次拜訪荷蘭動物用藥品主管機關（MEB Agency, Veterinary Medicinal Products Unit；VMPU）之動物用藥品管理部門就相關議題進行討論，期望就兩國之檢驗登記流程、疫苗安全性評估流程、及疫苗品質管理系統等議題進行交流。荷蘭動物疫苗品質皆回歸各製藥廠內部品管進行自主管理，並遵循歐洲藥典規範進行試驗，與美國、日本及我國皆有許多不同之處，參觀動物用藥廠之管理、動線及就檢驗技術進行討論，有助於提升我國動物用疫苗檢驗之品質與能量。

荷蘭瓦漢寧恩獸醫生物學研究所（Wageningen Bioveterinary Research），前身為中央獸醫研究所（Central Veterinary Institute of Wageningen UR），為重要動物傳染病的國家實驗室，具有操作高風險病原之實驗室（BSL-3 及 ABSL-4）、以及實驗動物設施，藉由參觀相關設施，可作為未來動物用藥品檢定分所相關實驗室及動物舍改進參考，以提升檢驗品質。

二、行程

日期	星期	工作紀要	地點
105/10/16 ～17	日	去程：桃園機場到阿姆斯特丹機場	
105/10/17	一	英特威動物藥品公司原廠(Intervet international b.v.) 研習內容：藥廠之生產動線及硬體設施	Boxmeer
105/10/18	二	英特威動物藥品公司原廠(Intervet international b.v.) 研習內容： 豬環狀病毒感染症之品管流程及效力評估方法 細菌性疫苗之品管流程及效力評估方法	Boxmeer
105/10/19	三	瓦漢寧恩獸醫生物學研究所（ Wageningen Bioveterinary Research） 研習內容： 實驗動物設施參訪及就設施設置方式進行研討	Lelystad
105/10/20	四	荷蘭百測（BioChek）生物科技公司原廠 研習內容：動物疾病快速檢驗及數據分析管理	Reeuwijk
105/10/21	五	荷蘭動物用藥品主管機關 The MEB Agency, Veterinary Medicinal Products Unit (VMPU) 研習內容：動物用疫苗檢驗登記制度及品質管理系統	Utrecht
105/10/22 ～23	六	回程：阿姆斯特丹機場到桃園機場	

三、 過程及研習內容

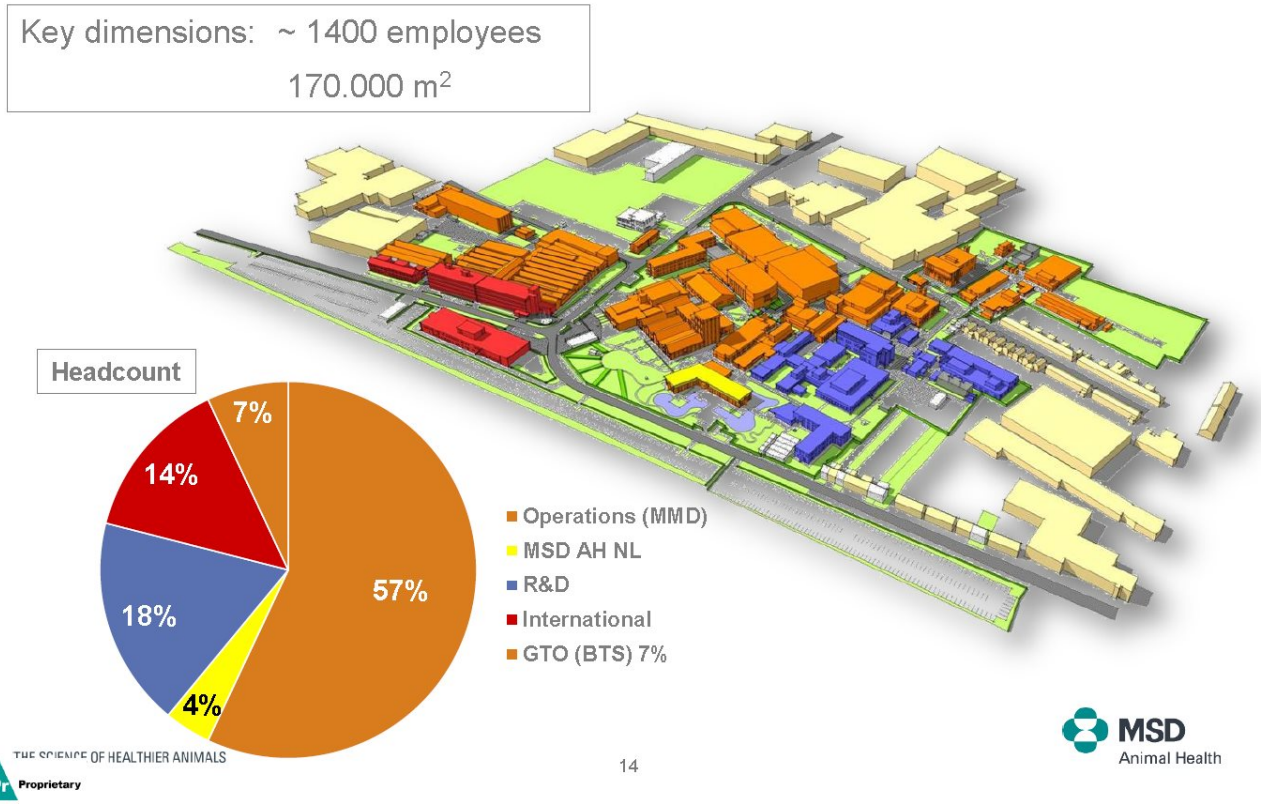
(一)英特威動物藥品公司原廠（Intervet international b.v.）

1. 10 月 17 日議程：

Monday 17 October 2016			Location PP03-1.013-I (Interlokaal 1)
Time (Hrs.)	Subject	Presenter	Title
13.00	Arrival at site	Pedro van den Acker	Sr. Specialist Quality Systems & Compliance
13.15	Welcome, openings meeting	Pedro van den Acker	
13.25	Safety Instruction	Rob van Ierssel	Director Operations IPT Live
13.30	Site presentation	Rob van Ierssel	
14.15	Quality Presentation	Jos van Vugt	Assoc. Dir Quality Systems & Compliance
14.30	Site tour	Bram Arts	Associate Specialist Automation
16.30	Close out day	Pedro van den Acker	

2. 原廠簡介

MSD（前身為英特威）動物藥品公司主要研發製造是在荷蘭 Boxmeer 鎮，為英特威的發源地，研發和製造獸醫產品（主要為疫苗產品）。超過 1,700 人在製造部工作，約 700 人在研發部工作。廠區共計 170,000 平方公尺，區分為製造與品管部門、行政部門、研發部門、國際事務部門、及產品包裝部門等。除了 Boxmeer 廠區外，鄰近城鎮還有動物試驗設施、SPF 蛋生產設施、物流中心等。所生產產品



85%為生物製劑，以豬用和禽用疫苗為大宗；15%為一般藥物，以牛用藥物為大宗。

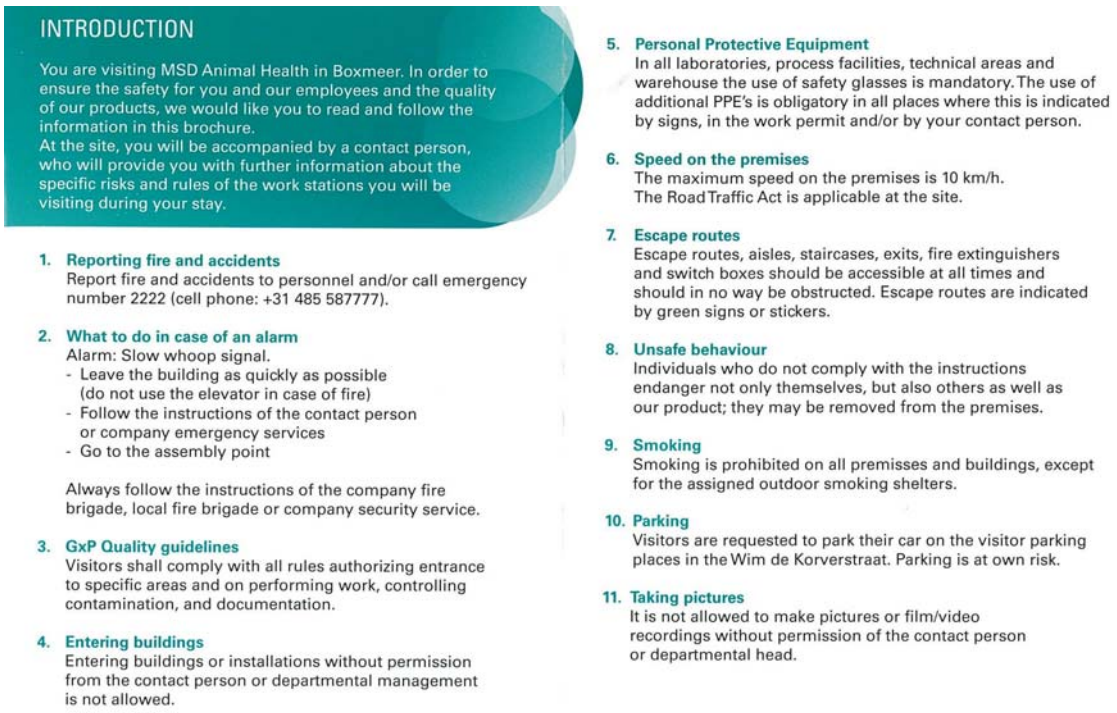
3. 藥廠之生產動線及硬體設施

(1) 安全管理

在進入廠區之前，訪客須先提供護照與服務台登記，並佩戴所提供之訪客識別證及門禁卡，進入會議室後，廠方先以簡報說明廠區的安全守則，重點如下：

- ✓ 爬樓梯緊握扶手
- ✓ 火災警報時立即離開建築物
- ✓ 依據指示穿著個人防護裝備，製造部和實驗室還需配戴護目鏡及防護鞋
- ✓ 於建築物間行走時，只能走在標示之人行路線
- ✓ 不可邊走邊使用手機
- ✓ 未經允許不得拍照

同時提供訪客專用宣導單張如下：



INTRODUCTION

You are visiting MSD Animal Health in Boxmeer. In order to ensure the safety for you and our employees and the quality of our products, we would like you to read and follow the information in this brochure.
At the site, you will be accompanied by a contact person, who will provide you with further information about the specific risks and rules of the work stations you will be visiting during your stay.

1. **Reporting fire and accidents**
   Report fire and accidents to personnel and/or call emergency number 2222 (cell phone: +31 485 587777).

2. **What to do in case of an alarm**
   Alarm: Slow whoop signal.
   - Leave the building as quickly as possible (do not use the elevator in case of fire)
   - Follow the instructions of the contact person or company emergency services
   - Go to the assembly point

   Always follow the instructions of the company fire brigade, local fire brigade or company security service.

3. **GxP Quality guidelines**
   Visitors shall comply with all rules authorizing entrance to specific areas and on performing work, controlling contamination, and documentation.

4. **Entering buildings**
   Entering buildings or installations without permission from the contact person or departmental management is not allowed.

5. **Personal Protective Equipment**
   In all laboratories, process facilities, technical areas and warehouse the use of safety glasses is mandatory. The use of additional PPE's is obligatory in all places where this is indicated by signs, in the work permit and/or by your contact person.

6. **Speed on the premises**
   The maximum speed on the premises is 10 km/h.
   The Road Traffic Act is applicable at the site.

7. **Escape routes**
   Escape routes, aisles, staircases, exits, fire extinguishers and switch boxes should be accessible at all times and should in no way be obstructed. Escape routes are indicated by green signs or stickers.

8. **Unsafe behaviour**
   Individuals who do not comply with the instructions endanger not only themselves, but also others as well as our product; they may be removed from the premises.

9. **Smoking**
   Smoking is prohibited on all premisses and buildings, except for the assigned outdoor smoking shelters.

10. **Parking**
    Visitors are requested to park their car on the visitor parking places in the Wim de Korverstraat. Parking is at own risk.

11. **Taking pictures**
    It is not allowed to make pictures or film/video recordings without permission of the contact person or departmental head.

廠區包含行政區、研發區、製造與品管區，各區域間每道門（包括戶外部分）皆有門禁管制，僅授權者才可進入，廠區道路將人員與各種工作車動線明確區分，並一開始即對訪客進行安全教育訓練，以維護人員安全，各項機制皆以勞工安全及生物安全為出發點設計。

(2) 品管部門

品管對象包含原料、半成品、種毒/種菌、抗原、安定性試驗樣品、研發部相關樣品，並負責相關技術轉移和驗證，以及實驗動物 3R 計畫。試驗方法包括微生物試驗、生物學試驗（in vivo / in vitro）、和一般物理化學試驗。

(3) 品保部門

品保部門職責包括：製造部及品管部批次紀錄審查、批次放行資料及 COA 文件之準備、協助並審查驗證方法及方法偏差、審查/批准 SOP 和製造說明書、符合性檢查及持續改進措施等。

(4) 產品監控

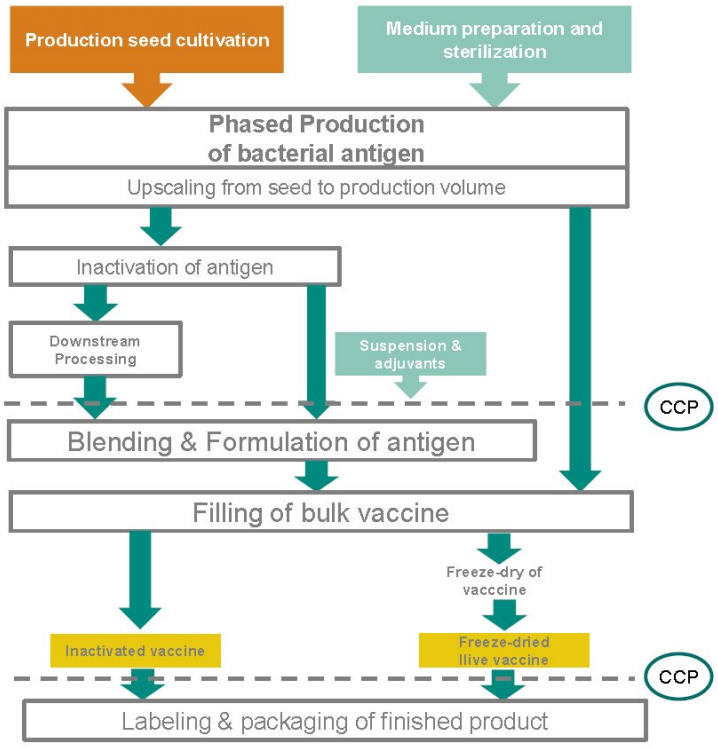
監控措施包括：生物製劑及化學製劑德安定性試驗管理及監控、通報和召回程序之協調、品官審核流程的管理、產品品質投訴的監控

和管理等。

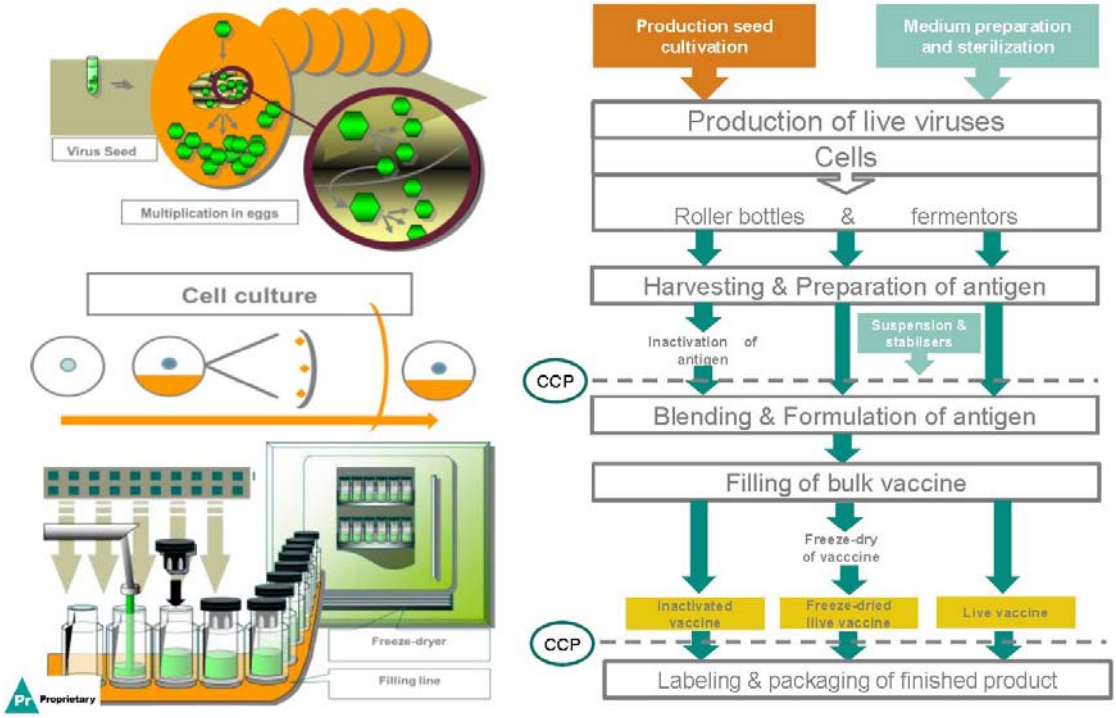
(5) 品質系統和 ISO 系統大致相同，包括：品質手冊、文件、變更管理、偏差管理、管理審查、內部稽核、供應商管理及外部製造等。符合性和改進管理包括：內部和外部稽核、查廠大約 2 至 3 年 1 次。

(6) 製造部大致可區分為活毒疫苗、不活化疫苗、活菌苗、死菌苗及化學製劑產品等，研發部門則大致以對象動物及病原種類做區分，例如 PCV2 疫苗的研發獨立於其中一棟建物，禽用病毒性疫苗研發則獨立於另一棟建物。品管實驗室則分散為 4 個區域，各自負責不同檢驗項目。

(7) 廠區內各個工作區域，包括研發實驗室、品管實驗室、製造區，皆設置透明玻璃窗，雖本次無法進入實驗室或製造區參觀，亦未獲允許於場區內拍照，但站立於戶外即可一目瞭然人員工作情況，透明化管理可讓訪客對其品質管理感到信服。



上圖為細菌性疫苗製造流程



上圖為病毒性疫苗製造流程

與原廠接待人員合影，左起為台灣英特威代表林岳賢經理、Rob van Ierssel (Director Operations IPT Live)、Jos van Vugt (Assoc. Dir Quality Systems & Compliance)、Pedro van den Acker (Sr. Specialist Quality Systems & Compliance)

4. 疫苗品管流程及效力評估方法

(1) 10 月 18 日議程：

Tuesday 18 October 2016			**Location** PP03-1.013-I (Interlokaal 1)
Time (Hrs.)	Subject	Presenter	Title
09.00	Arrival at site		
	Safety test for batching test		
09.05	Nobivac KC – In Taiwan, we can't use dogs for safety test. So we need to develop a safety test by use laboratory animal instead of dogs.	Ton Jacobs Eric Klaasen	Prin. Scientist, Research Science Prin. Scientist, Research Science.
	Potency test for batching test		
10.00	1. Innovax-ILT: How we perform ILT potency test for the batching release?	Harry Glansbeek, eventually WEBEX with Salamanca site.	Assoc. Dir, Quality Control, Bio Analytical Tech Support EU
11.00	2. Porcilis PCV M Hyo & Porcilis PCV ID: Why there are 2 kinds of potency test for the 2 products? If it is possible to use the same potency test of Porcilis PCV M Hyo to perform potency test of Porcilis PCV ID (In Taiwan there is no AlphaELISA machine to perform potency test of Porcilis PCV ID)?	Melanie Sno	Associate principle scientist, Research Science
12.00	Lunch		
13.00	3. Porcilis ColiClos: We need more detailed directions for performing "estimation of Clostridium Perfringens type B antibody level" - potency test SOP/QC.038F in Taiwan. If there is a QC person can support us to perform this potency test in Taiwan?	Maarten Witvliet, eventually WEBEX with Milton Keens site.	Prin. Scientist, Research Science
14.00	4. Porcilis ColiClos: How you do potency test for E.coli part?	Maarten Witvliet	
15.00	5. Nobilis E. Coli : The ELISA data of antibody titer (batching potency test in Taiwan) is not really satisfied. If there is a QC person can support us to perform this potency test in Taiwan?	Roy Bouw Gaby Dekkers	Manager Quality Sr. Tech, Quality Control
16.00	Other discussion points	T.b.d.	
16.30	Close out		

(2) 會議目的：

荷蘭在動物用疫苗的品質管理規範係遵循歐盟標準，在歐盟國家販售都沒問題，但我國因動物疫苗逐批檢驗之緣故，加上動物用藥品檢驗標準有許多已老舊缺乏彈性，在進口疫苗的檢驗上常會遇到瓶頸。本次與英特威藥廠的研發及品管人員面對面的交流，能更了解他們產品設計及檢驗方式設計的目的及緣由。

(3) 安全性試驗

a.小動物細菌性疫苗（以 Nobivac KC 為例）

我國小動物疫苗（非經濟動物疫苗）檢驗標準為以替代動物進行安全性試驗，效力試驗則以審查原廠資料作為替代，不另外進行測試。惟英特威公司之 Nobivac KC（犬博德氏菌苗）於台灣進行新藥登記時，以替代動物（小鼠）進行安全性試驗皆不合格（試驗動物未全數存活），故提出討論。

原先犬用疫苗在原廠要在犬隻做試驗，但歐盟的新的規定可以不用做了,因此目前 Nobivac KC 也沒有再以犬隻進行安全性試驗。之前之所以建議以豬做為替代動物，是因為豬隻對博德氏菌感受性高，但在台灣評估過後認為以豬做為犬隻的替代動物並不適合（豬隻體型較犬隻大）。建議原廠建立天竺鼠作為替代動物、以鼻腔接種疫苗之模式、並算出合理的接種劑量，若有相關數據可提出，台灣方面即可據以修改安全試驗之替代動物模式。

(4)效力試驗

a. 豬第二型環狀病毒疫苗（PCV2）

目前英特威公司的 PCV2 疫苗（Porcilis PCV）在我國的檢驗標準是在雞隻免疫 4 週後，以 ELISA 測定抗體是否陽轉。該公司在 PCV2 疫苗還有 2 項較新的產品，包括 Porcilis PCV M Hyo 和 Porcilis PCV ID，未達成實驗動物減量目的，前者效力試驗可以 ELISA 直接測定疫苗之抗原含有量，後者則使用較新技術「AlphaLISA」方法檢測抗原含量，可省時又省力；惟 AlphaLISA 設備極為昂貴，檢定分所不可能僅為特定廠商之特定產品購置該設備，原廠亦不可能僅為了在台灣進行檢驗登記，就針對該產品再研發另一種檢驗方式，因此 Porcilis PCV ID 產品要在國內進行登記尚需多方面評估。

b. 豬大腸桿菌梭菌雙價菌苗（CPEColi）

梭菌部分請原廠提供 L_0 及 L_+資料及數據，以及以兔之進行替代模式之數據。EColi 部分原廠 ELISA 的特異性很好，若要在台灣進行相同的 ELISA 試驗就要提供試劑和 SOPs；另一方面是否有針對 EColi 的商品化測試套組？這部分將再由檢定分所進行

評估。

c. 家禽大腸桿菌（CEcoli）

英特威的家禽大腸桿菌次單位疫苗（Nobilis E. Coli）檢驗疫苗力價須使用原廠提供 ELISA 套組，原廠雖已提供套組並由本分所檢驗完成，惟原廠不願提供統計計算軟體，亦不能接受替代方案（例如以其他方式統計比對），理由是原廠認為數據分析必須使用 IT 部門提供且管制的軟體，是因品管部門所有使用的設備、試劑、乃至於軟體都是已經確效過的，因此無法接受使用任何未經確效的替代方案。

廠區會議室外觀

於品管實驗室外與品管經理 Roy Bouw 合影

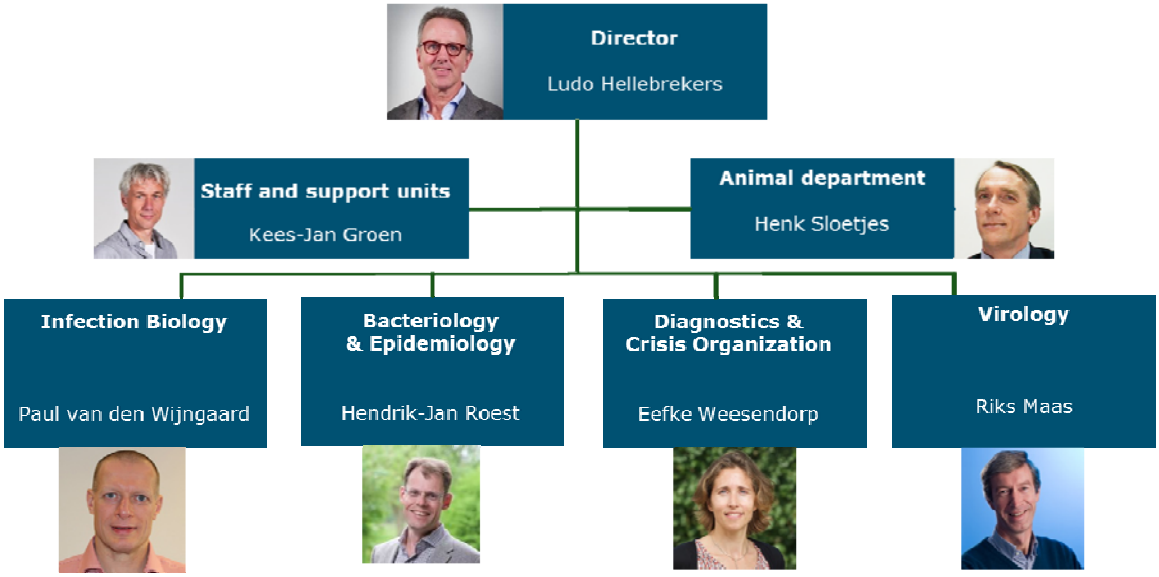
(二)瓦漢寧恩獸醫生物學研究所（Wageningen Bioveterinary Research）

1. 10 月 19 日議程
   - 09:00 Welcome
   - 09:15-10:00 簡報介紹 WBVR
   - 10:00-11:00 疫苗檢驗相關討論
   - 11:00-13:00 動物舍施介紹及參訪
   - 13:00-14:00 午餐及討論
2. 沿革

   瓦漢寧恩獸醫生物學研究所(Wageningen Bioveterinary Research；WBVR）隸屬於瓦漢寧恩大學暨研究中心（Wageningen University & Research），前身為中央獸醫研究所（Central Veterinary Institute of Wageningen UR）。

   1904 年成立國家血清研究所，位於鹿特丹；1929 年成立國家獸醫研究院，位於阿姆斯特丹；1959 年國家血清研究所和國家獸醫研究院合併為中央獸醫研究所（Centraal Diergeneeskundig Instituut）。1972 年和 1982 年前述兩者先後遷移至 Lelystad；1994 合併幾個單位成為 ID-DLO（Dutch Institute for Animal Health and Science）；1999 年更名為 ID-Lelystad，成為 Wageningen UR 的一部份。後來陸續變更為 CIDC-Lelystad、動物科學團隊，於 2008 年，CIDC-Lelystad 合併感染性疾病部門成立中央獸醫研究所（CVI of Wageningen UR）；2016 年 9 月 6 日再度更名為瓦漢寧恩獸醫生物學研究所（Wageningen Bioveterinary Research）。
3. 組織編制

   WBVR 設有一名所長，轄下分 4 個業務組，包括感染生物學組、細菌與流行病學組、診斷與應變組、病毒學組，另設有動物部門，負責管理實驗動物設施與高防護實驗室，員工總數為 230 人。



4. 業務範圍

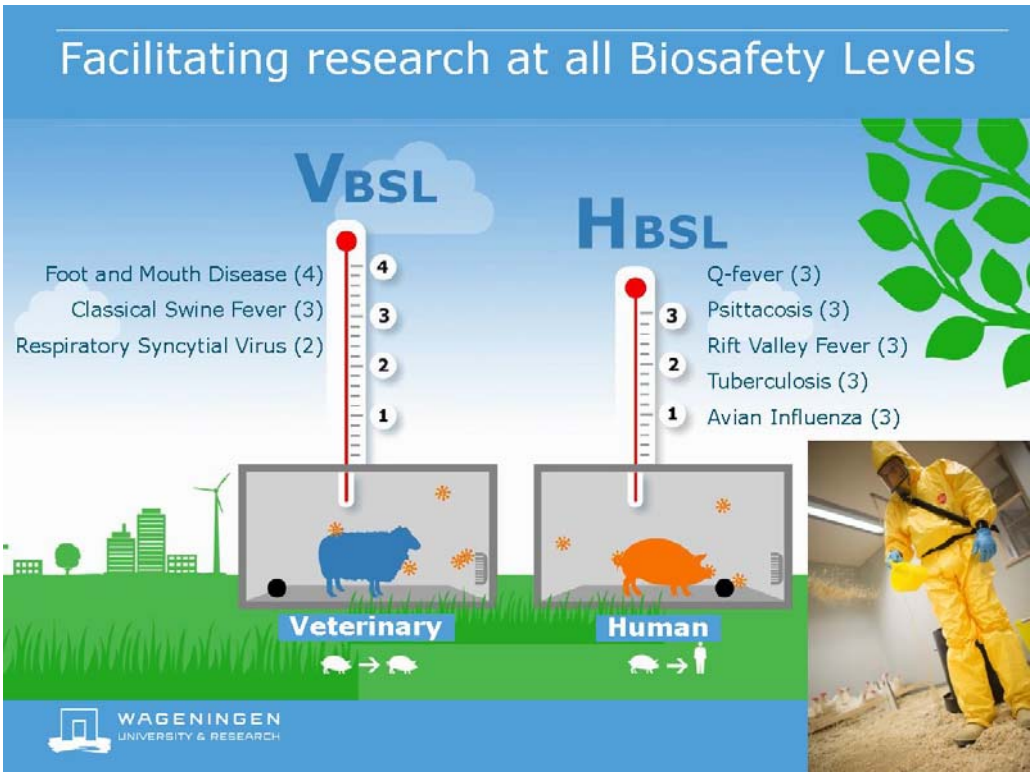
(1) WBVR 為國家級參考研究機構，為國家傳染病診斷實驗室，並為彎曲桿菌、假性狂犬病、Q 熱及馬傳染性子宮炎之國際參考診斷實驗室。

(2) 符合 ISO 9001 和 ISO 17025 品質系統，提供經濟部動物疾病防控諮詢、疫情爆發時 24 小時全年無休任務編組、與動物藥廠合作研究、技術移轉等。

(3) 研究範圍包括診斷方法建立、動物模式建立、臨床試驗、抗藥性研究、禽流感防治研究、動物疫苗研發以及提供動物試驗服務等

5. 研究設施

實驗室包括細菌學、病毒學、病理學、分子生物學、免疫學、魚病學及生物安全第三等級（BSL-3）實驗室；動物設施包含農場動物及實驗動物舍、人類 BSL-1~3 級和動物 BSL-2~4 級動物舍，以及基因改造產品動物舍。動物種類包括：豬、牛、羊、禽、伴侶動物、嚙齒類、羊駝及其他野生動物，品質分級包括傳統、SPF、DPF (Designated pathogen free)、剖腹產來源以及 Germ free 等。



生物安全分級依該病原之 RG 等級而定，並區分人類及動物之風險：

Risk group	病原性	對人類的預防/治療	舉例	生物安全等級	可在 WBVR 操作	
					獸醫	人類
1	-	NA	乳酸桿菌	BSL-1	+	+
2	+	+	金黃色葡萄球菌	BSL-2	+	+
3	++	+	禽流感	BSL-3	+	+
4 (動物)	+++	-	口蹄疫	BSL-4	+	-
4 (人類)	+++	-	伊波拉	BSL-4	-	-

以人類 BSL-3 實驗設施為例，生物安全管控的方式包括：高效濾網（空氣）、化學滅菌及高溫滅菌（廢水）、高溫高壓滅菌鍋（墊料）、化製槽（屍體）以及個人防護裝備和檢疫（人員）。

排氣管線與 HEPA

廢水滅菌處理系統

穿牆式滅菌鍋

化製槽

人員防護裝備

門禁系統（偵測指紋）

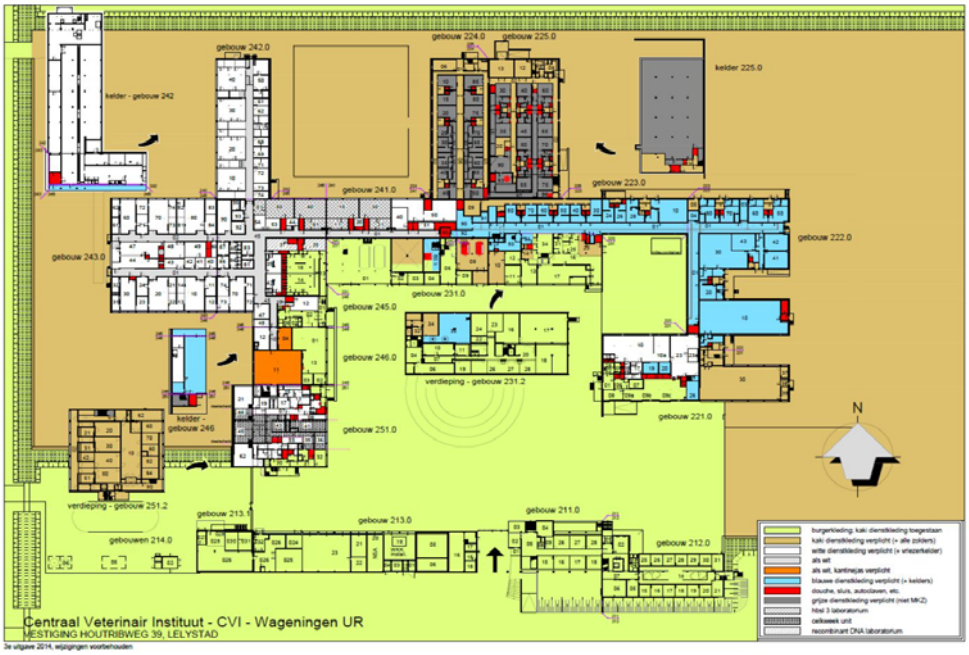
（因場區禁止拍照，以上圖片均截自 WBVR 簡報內容）

6. 動物設施參訪

WBVR 動物試驗設施區域皆為管制區，以風險等級區分為 3 個區域，每個區域穿著之衣服顏色接不相同。本次參觀「卡其區」為風險較低區域，該區域工作人員皆須至衣物間領取清洗消毒好之卡其色工作服，才可進入。所有進入管制區人員都必須簽署一份聲明書，目的為防止外來動物病原（特別針對口蹄疫）污染場區，以及防止將管制區內病原帶出感染民間牧場，所有人員都必須恪守 24 小時內不得接觸口蹄疫感受性動物之規定。

其中一間參觀之動物設施已設置超過 30 年，仍持續運作並維持設備穩定及環境整潔，其軟體、硬體管理上可見到許多設計值得學習，例如半球面型的窺視窗，可大範圍觀察飼育室中動物情況；飼育室門上表單已具有磁性的透明文件夾固定，可維持整潔美觀；傳遞箱除紫外燈殺菌型式外，亦有浸泡桶型式；屍體以化製方式處理，不僅可確保滅菌完全，亦較節能；不論是工作區域、設備層、汙染區皆維持很高標準的整潔。

此外實驗動物大多為平飼，飼育空間注重環境豐富化，動物棲息於飼育室中十分放鬆，由窺視窗觀察動物時，即使距離很近，也不見動物出現驚慌緊迫之神色，可知其動物福利落實並符合動物需求。



場區平面圖，卡其色區域為較低風險區域，本次參觀一間目前淨空之動物設施。

豬舍

雞舍

動物飼育室的窺視窗設計成半球面體，人員在走道探視動物可有大角度之視野。

解剖室

（因場區禁止拍照，以上圖片均截自 WBVR 簡報內容）

於 WBVR 會議室與動物部門主任 Henk Sloetjes 合影

於 WBVR 會議室與所長 Ludo Hellebrekers 及 Ivo Claassen 博士合影

(三)荷蘭百測（BioChek）生物科技公司原廠

1. BioChek 成立於 1997 年，專門生產製造家禽和豬隻疾病診斷試劑套組，可提供畜牧場獸醫或業者其豬群和禽群的抗體狀態，使畜牧業者能掌握動物群體免疫狀態，亦可於場內出現健康狀況異常訊息時及時進行防疫措施。除牧場外，其主要服務對象還包括獸醫學實驗室、育種公司、SPF 蛋牧場以及疫苗公司。其產品中 AI（CK121）和 NDV（CK116）抗體檢測套組已通過 OIE 認證。BioChek 總公司位於荷蘭，美國東部有分公司，另產品的研發及生產係位於英國倫敦，荷蘭總公司負責所有的物流配送。
2. 就本分所實驗動物研究系在使用 BioChek 的 ELISA kit 時所遇到的一些問題，提出於會議討論。
   (1) 使用 FADV I (Fowl Adenovirus Group 1) Antibody test kit，在 1 日齡、3 週齡、5 週齡出貨雛雞血清檢測，所有均為抗體陰性，繁殖雞群在 35 至 36 週齡前抗體檢測結果亦皆為陰性，惟此時間點之後平均會有 5%的陽性檢出（樣本數為 68 或 92 隻），此結果該如何判讀？

   結論：無法確定可能造成此結果的原因，可評估是否將陽性血清分讓送至總公司，可藉此改善所生產 ELISA kit 的效能。惟血清分讓需經過申請及文件簽署，亦可先將檢測出之數據資料寄至總公司，檢視問題所在。
   (2) 是否可以生產雞馬立克病（Marek's disease）或雞病毒性腎炎（Avian Nephritis Virus）的 ELISA kit？

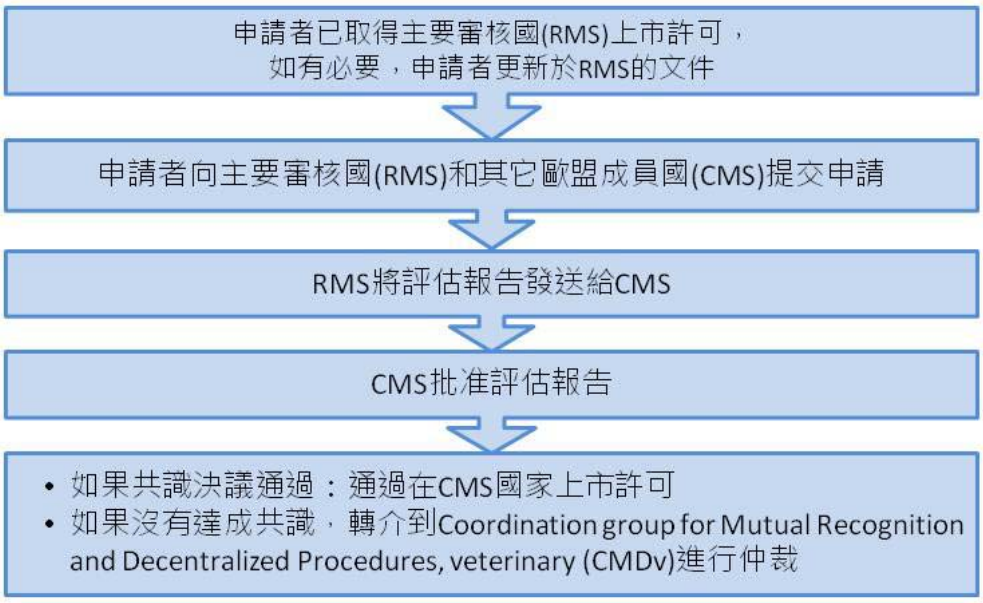
   結論：MD 的 ELISA kit 自 20 年前即開始研發，但因該疾病非體液性免疫，測不到細胞免疫所產生的抗體，因此尚未成功生產出產品。ANV 的部分研發部門確實有在進行 ELISA kit 研發，可先確認需要的型別（type 1~8）再與該公司進一步接洽。

與 Eric van Esch (技術部門主任)及 Tiede Bijlsma (技術支援經理)於該公司內會議室合影

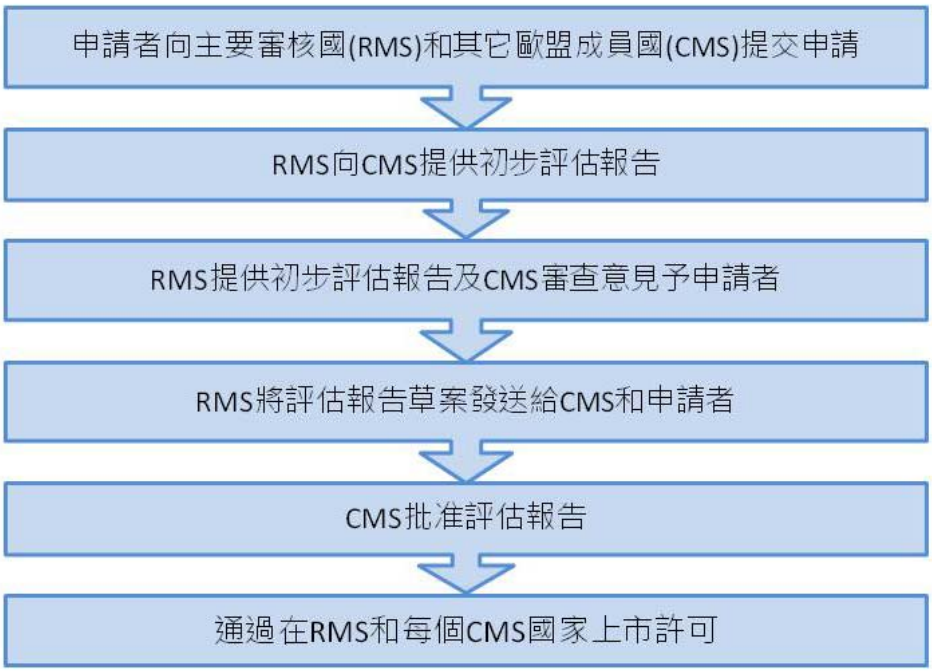
BioChek 荷蘭總公司大門

(四)動物用藥品主管機關：Medicines Evaluation Board (MEB)之中的 Veterinary Medicinal Products Unit (VMPU)

1. 10 月 21 日議程
   - 10:00-10:10 雙方人員互相介紹
   - 10:10-10:35 動物用藥品檢定分所簡報（李淑慧分所長）
   - 10:35-10:55 VMPU 簡介（José Jonis 博士）
   - 10:55-11:20 荷蘭動物用藥品審查流程及檢驗（Tom van der Heijden 博士）
   - 11:20-11:50 綜合討論
2. 機關簡介：
   (1) 荷蘭自 1986 年起開始進行動物用藥品登記業務，主管機關為經濟部，自 2005 年起隸屬於 CBG - MEB (College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board)，主要為其中獸藥產品部門 Veterinary Medicinal Products Unit (VMPU)所負責。VMPU 為 MEB 的一部分，但屬於不同的法定組織結構，和我國由衛方和農方分別管理有很大不同。其權責包括動物用藥品製造／進口／貿易／批發／零售之授權、VMP 出口認證、相關決策幕僚、藥物主動監測、飼料添加物以及相關業務諮詢等。
   (2) 統計至 2016 年 10 月 10 日止，已檢驗登記 2,604 項獸藥產品，每年並新增 100~125 項；申請科學評估者有 200~300 項，申請變更案件有 500~600 項，許可證已有 2,500 項，批次放行疫苗有 1,310 批。
   (3) 組織成員：包括 3 名高階登記專案主持人（同時身為為歐盟動物用醫藥品委員會 CVMP 成員）、12 名登記專案主持人、3 名臨床評估員、7 名登記專案官員、1 名藥物警戒協調員、1 名許可證協調員、2 名許可證管理員及 1 名單位主管。
3. 荷蘭動物用藥品評估及登記
   (1) 上市許可程序
   申請動物用藥品上市許可，可透過國家程序、相互承認程序、分散式審查程序、以及集中式審查程序等途徑。
   a. 相互承認程序（Mutual Recognition Procedure；MRP）



b. 分散式審查程序（Decentralised Procedure；DCP）



c. 集中式審查程序（Centralised procedure）

集中式審查程序於 1995 年開始實施，申請者可直接向歐洲藥品

管理局（EMA）申請上市許可，通過後可獲得在所有歐盟成員國以及包括挪威，冰島和列支敦士登等國家有效的上市許可。

相關規定可參照歐洲藥品管理局網站：

http://ec.europa.eu/health/authorisation-procedures-centralised_en

(2) 評估

荷蘭就動物用藥品進行評估的項目包括：品質、效力（生物等效性）、動物安全、消費者安全、使用者安全、環境安全等，尤其注重抗藥性、消費者及環境安全等項目。

(3) 潛在嚴重風險（Potential Serious Risk, PSR）的可能性

消費者：有關停藥期，無法提供足夠程度證明

使用者：預防措施無法將風險降低到可接受水平

動物：未有足夠證明其藥品效力、於安全性上是否有不可接受之風險，或未於標籤上清楚標示，以及生產和控制流程是否保證不會發生嚴重缺陷

(4) 評估程序

a. MEB 階段：所有的藥品登記專案主持人（RPL）、歐盟動物用醫藥品委員會（CVMP）成員、CMDv 成員、單位主管以及內部評估人員每週都要召開會議，RPL 必須在案件驗證階段提出程序報告，以對申請文件做一致性的評估。

b. 第二方意見：如有潛在嚴重風險的可能，由科學委員會以及 7 名外部獨立成員以及 MEB 秘書處提供第二方意見，科學委員會將其正或反向意見回饋給首席獸醫官。

c. 最終判定：由首席獸醫官（CVO）判定核准上市，或無法判定時轉介至歐盟委員會（European Commission）進行進一步評估和判定。

(5) 所有藥物評估皆以歐盟標準規範，檢驗登記時僅以文件審查為主，廠商自負檢驗；如遇有爭議項目，即委託第三方單位檢驗，例如 WBR。檢驗登記過後即可販售，無逐批檢驗，亦無官方檢驗單位。藥廠以 GMP 為標準來管理，每 3 年查廠一次。所有藥品評估項目、檢驗方法、文件審查紀錄皆公開在 European Commission 網頁供全

世界下載或查閱，資訊公開透明值得效法。

4. 問題討論

(1) 新的產品登記時，須準備哪些資料呢？

相關規範列於 EudraLex - EU Legislation，Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use 項下，可隨時至該網頁查詢最新版規範。網址：http://ec.europa.eu/health/documents/eudralex/vol-6_en

(2) 有官方的動物用藥品檢驗機關嗎？

荷蘭官方沒有在進行動物用藥品檢驗，都是由廠商自行負責品管檢驗，主管機關僅進行文件審查，若有遇到具爭議性的案件，則尋求第三方公正單位，例如瓦漢寧恩獸醫生物學研究所進行檢測或試驗。

(3) 對於動物藥廠的相關規範為何？是 GMP 或是 cGMP 呢？

荷蘭（以及其他歐盟）的藥廠，皆依循 GMP 規範，每 3 年會進行一次查廠。

(4) 荷蘭政府會針對國外進口疫苗進行檢驗嗎？

所有疫苗管理皆依循歐盟規範，若為歐盟國家進口，不需另外進行檢驗，但若發生重大疫情，需自歐盟以外國家進口緊急防疫用疫苗，則另外進行專案討論評估，此部分流程即因案件而異。

(5) 基因改造動物用藥品在申請登記時所需文件為何？

包含對象動物、非對象動物、環境安全性、毒力回歸試驗、風險評估等資料。另此類藥品是以集中式審查程序（Centralised procedure），可在歐洲藥品管理局（European Medicines Agency）的獸藥產品公開評估報告（European public assessment reports, EPARs）網頁查詢，所有取得許可證的藥品皆已刊登其上，可搜尋特定基因改造產品，瀏覽該藥品評估歷程。網址：http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_epar_search.jsp&mid=WC0b01ac058001fa1c

(6) 要如何評估基因改造產品對動物和環境的安全性？

依案件及製劑型式而異，相關規定可在歐洲藥品管理局（European

Medicines Agency）之生物製劑一般性指引中查詢。網址：http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000374.jsp&mid=WC0b01ac058002ddc5

於會議室與 Tom van der Heijden 博士及 José Jonis 博士合影（兩位博士皆為 Regulatory Project Leader）

MEB 機關門口

四、 心得與建議

1. 荷蘭身為農業大國，不僅畜牧業發達，並且十分注重動物福利，以經濟動物、實驗動物和野生動物皆不怕人的特性來看，應是荷蘭人民尊重動物並且以動物的角度來達到動物福利的目的，一旦動物覺得舒適，生長表現就會更好。雖不可否認的是由圈養改為放養確實可能增加防疫上的問題，但只要面對問題並以合理的方式（例如加強生物安全管理及疫苗免疫）長久來看品質與獲利皆能提升。
2. 本次研習對象包含 1 個公務單位、1 個學術單位、1 個藥廠和 1 個檢測試劑研發公司，對其系統運作的縝密度感到印象深刻，他們能夠對目標有明確認知，並針對所有可能影響結果的因子用嚴密的方式進行管控，而各項因子又能環環相扣而不脫鉤，如此才能在所有員工之間落實執行。
3. 承上，因各個單位的業務屬性不同，所著重的目標也略為不同，例如獸藥主管機關所著重的就是資訊安全，對於廠商資訊及審核過程中的保密資訊皆嚴防戒備，但針對已完成並且可公開的資訊，皆能及時公告於網路供全世界查閱。學術單位及藥廠則著重勞工安全及生物安全，並且致力於試驗品質的管理認證與提升。檢測試劑公司因其主要製造部不在荷蘭，因此當地廠房主要做為教育訓練推廣及全球物流據點，進貨／出貨即為重點項目。由此顯見確立自身屬性及核心任務並據以精進，方能使整個管理系統趨近完美。
4. 本次參訪單位不論是新設建築或既有的老舊建築，皆能維持良好運作及環境整潔，除了投注經費在新設建築、維護既有建物及設備之外，想必也在維持環境整潔美觀上投資了許多，然而這卻可能是國內各機關單位公司最容易忽略的部分。
5. 本次接待我們的人員大都是高階人員,可以想見他們對國際合作的重視。雖第一印象會覺得荷方人員嚴肅而高傲（尤其是公務單位），然而實際表現出來的卻是在專業上嚴格、在待人上親和；其守時與誠實透明的態度，能讓人自然而然的尊重且信服，想必這是我國公務單位最需要學習仿效的地方了。
6. 藉由此次參訪研習發現荷蘭的獸醫科技在歐盟扮演極重要的地位，尤其是英國脫歐後，更顯得荷蘭的重要，尤其是荷蘭動物用藥品主管機關（MEB）完善管理度與經驗，值得我國效法。瓦漢寧恩獸醫生物學研究所擁有最新生物安全等級的三級及四級實驗室， 具有許多診斷及操作新浮現動物及人畜共通傳染病試驗研究的經驗，其獸醫研究的成果在全球

已與美加並列，未來於台荷農業合作的架構下，建請持續支持雙方專家互訪及舉辦國際研討會，以培養我國動物用藥品及新浮現動物及人畜共通傳染病方面的專才。

五、 致謝

感謝 Veterinary Medicinal Products Unit of Medicines Evaluation Board、Wageningen Bioveterinary Research、Intervet international b.v.和 BioChek 公司百忙中安排接待本分所參訪人員，並就所提出議題進行深度討論。感謝行政院農業委員會提供經費並核准本次參訪行程。

六、 附錄

(一)英特威動物用藥品公司荷蘭原廠簡介（MSD Animal Health The Netherlands）

(二)Wageningen Bioveterinary Research 機構簡介

(三)Wageningen Bioveterinary Research 動物設施簡介

(四)BioChek 公司簡介

(五)MEB Veterinary Medicinal products Unit 機關簡介

(六)MEB 獸藥產品評估方法簡介

Welcome to

MMD Animal Health The Netherlands

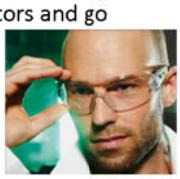
Technology Center for Biologicals

Presenter: Rob van Ierssel - Director Operations IPT Live

Visit Taiwan Authorities: I-Ting Ko and Shu-Hwae Lee

17-18 October 2016

Basic Safety Tips Everyone Can Use



- Always hold handrail on stairways. Only carry what you can safely handle with one arm.
- In case of fire alarm follow the instructions of your contact person (leave building asap and don't use elevators and go to the assembly point)
- Wear PPE's when applicable (look at the signs) (in production and lab area's safety glasses and safety shoes are mandatory)
- Use the designated marked paths when walking between buildings.
- Do not use mobile phones when walking on site.
- Smoking is only allowed in the designated area's
- It's not allowed to make pictures without permission from your contact person

- **Keep Eyes On Task**
- **Keep Mind On Task**

Fire / First Aid

- MSD-AH has his own First aid and fire department
- Emergency numbers:
  - Internal: 2222
  - Mobile: 0485-587777
- Assembly point

Content

MSD Animal Health

MSD AH NL Operations

MSD AH CoE Quality Operations

Process overview

MSD

MSD

Human Health

Major Therapeutic Areas
- Cardiovascular
- Diabetes & obesity
- Infectious disease
- Neurosciences & ophthalmology
- Oncology
- Respiratory & immunology
- Vaccine-preventable diseases
- Women's health & endocrine

Animal Health

- Ruminants
- Poultry
- Companion animal
- Aquaculture
- Swine

Animal Health Specifics

MSD Animal Health

- A leader in
  - Cattle segment
  - Poultry segment
  - Swine segment
  - Aquatic segment
  - Sheep segment
- Top 4 of Companion Animal segment

- Broilers, breeders and layers
- Health is mainly economically driven

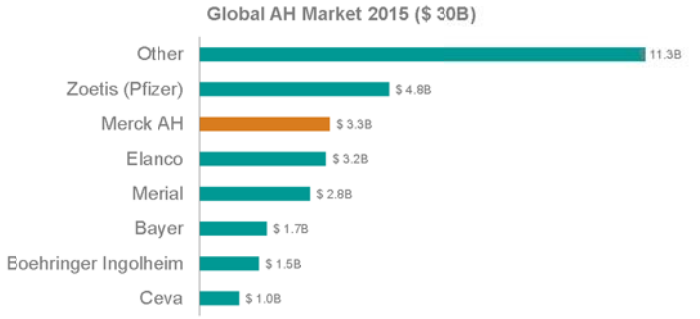
- Sows and fatteners
- Growth in respiratory vaccines segment

- Cattle (dairy & beef), sheep and goats
- Efficient production and control of disease

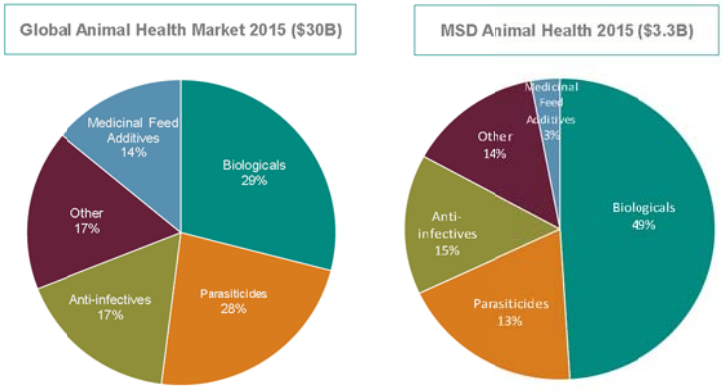
- Dogs, cats and horses
- Fastest growing segment over the past 15 years

- Emerging industry, fast growing
- Diseases vary with water temperature

MSD Animal Health – #2 Worldwide



Global Animal Health Sales by Product Category



Source: Vetnesis and internal sales data

Animal Health is a very attractive industry

In the Animal Health World ... How does working in the Animal Health World look like?

Compliance	Same GMP principles and guidelines requesting the same compliance level (additional addendum specific for veterinary use) Global Policy: Merck Quality Manual and as chapter 36 the Animal Health Quality Manual
Regulatory	Competent Health Authorities: shared (IGZ, FDA) / separated (VMD, USDA) Cooperation is influenced by overall animal welfare: dialogue approach based on risk assessment Customers: different risk profile (veterinarians)
Production	Process: Mix – Blend – Fill in controlled facilities (acc. to Annex 1), trained personnel, qualified equipment and validated processes using approved materials Multiple technology platforms per site Presentations: more multi dosage forms in AH
Supply	End-to-End ownership of product supply from Raw Materials to shipment of Final Packed Product Commercialized supply channel, strong cost competiveness
Cost basis	smaller margins → need to be lean and efficient → multi-use process lines → smaller investment volumes, stringent project timelines → New Product Introduction: shorter Development Cycle times

Content

MSD Animal Health

MSD AH NL Operations

MSD AH CoE Quality Operations

Process overview

Global Animal Health Manufacturing Facilities

AH Boxmeer Site

Key dimensions: ~ 1400 employees
170.000 m²

Headcount

Multiple-Site Organization


Boxmeer


Production Facility de Bilt


Production Facility Cologne

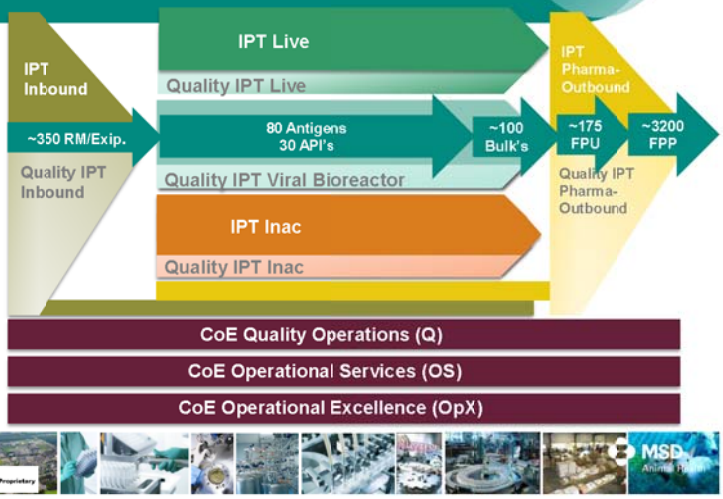

Animal Testing Facility Stevensbeek


SPF-egg Facility Houten

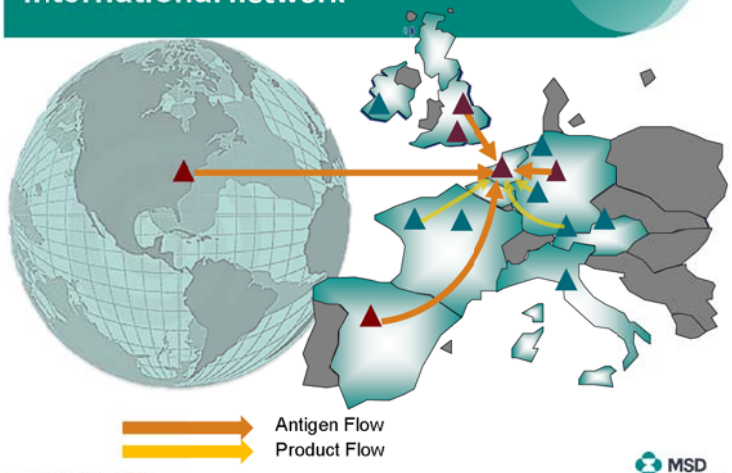

Logistics Center Boxmeer

Operations Leadership team

Value stream



International network

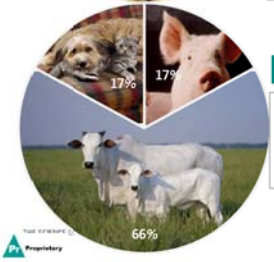


Product portfolio

Biological products

- Sales (85%)
- Top Products:
  PCV Porcilis*
  IB 4/91*
  PRRS
  DHPPi **

*Joint effort with Salamanca
** Joint Effort with Burgwedel



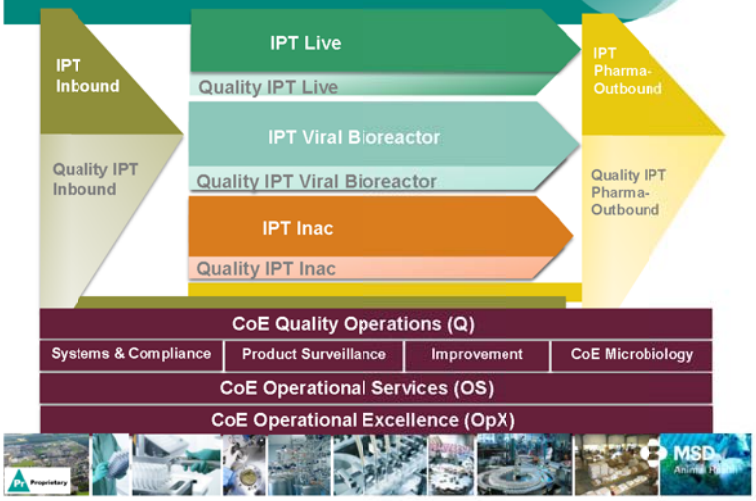
Pharmaceutical products

- Sales (15%)
- Top Products:
  Mastijet Forte
  PG 600
  Folligon/PMSG

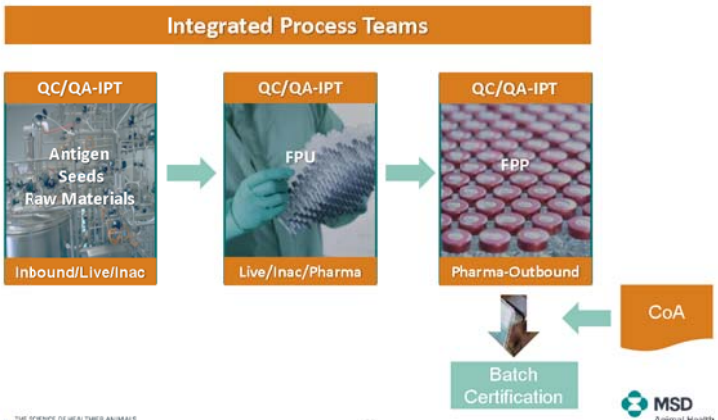
Content

- MSD Animal Health
- MSD AH NL Operations
- MSD AH CoE Quality Operations
- Process overview

Value stream



Quality Control / Quality Assurance



Quality Control Operations

Responsibilities

- Quality Control on Raw materials, API's, Primary packaging materials, Seed materials, IPC, Antigens, FPU, Stability samples and R&D related samples
- Trending and method life cycle management
- Technology transfer and validation
- 3R program (Reduce, Refine and Replace Animal testing)

Test Methods

- Microbiological testing (Building PP030)
- Biological testing (in vivo / in vitro) (Building PP024)
- Physical / Chemical testing (Building PP055, tower)

Quality Control - Locations

Quality Assurance

Review and release

- Batch review of production and QC documentation
- Preparation of batch release proposal
- Preparation of batch documentation for Certificate of Analysis
- The Qualified Person is responsible for batch disposition (Antigen/ FPU or FPP)

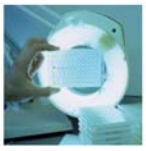
Support to Production and Quality Control Departments

- Assistance and Quality Review in validation procedures, change & deviation procedures
- Review & approval of standard operating procedures and manufacturing instructions
- Compliance checks
- Working together on continuous improvement on quality related issues (shop floor)

Product Surveillance

- Management and surveillance of the Ongoing Stability Program of Biologics and Pharmaceuticals
- Coordination of the Health Authority Notification process & Recalls
- Management of the Product Quality Review process
- Management and surveillance of the Product Quality Complaints for site Boxmeer






Quality Systems & Compliance

Quality and Compliance oversight of the Site Boxmeer Quality Management System and Ownership of Key Quality Systems:

- Quality manual
- Documentation
- Change control
- Deviation management
- Regulatory Inspections
- Internal Auditing
- Supplier management
- External manufacturing

Compliance and improvement focused management:

- Audit program (internal and external)
- Inspections (Regulatory Health Agencies / Corporate audits)
- Tier 5 – Site Quality Council and quality metric's

Quality Improvement

- **Facilitate in realization of our Strategy: The Perfect order by Creating Stability and Compliance**
- **Responsibilities**
  - Eliminate non planned events
  - Enhance CAPA effectiveness
  - Operationalizing Quality, fair amount of work for employees and a reliable partner for Customer and Clients

- **How (practice and teach)**
  - Lean and Six Sigma Methodology
  - Quality Risk Management
  - Tier process (organisational and strategically performance management system)

Center Of Excellence Microbiology

Knowledge & Expertise driven by CoE Microbiology

MSD AH Large Molecules

Development

- Development & Validation of Microbiological tests
- Development of microbial rapid methods
  - Rapid Method Identifications (MaldiTOF biotyping)
  - Rapid Method Sterility testing (BD Bactec CO2 detection)
- Validation of Cleaning Agents & Disinfectants
- Preservative efficacy testing
- Validation of cleanroom gowns, attributes and disposables
- Delivery of microbial freeze dried reference test strains

Alignment and Centralisation

- Release testing / central merger of bioindicators
- Growth Promoting Properties testing / central merger of media

Practical support

- Problem-solving and Education

Content

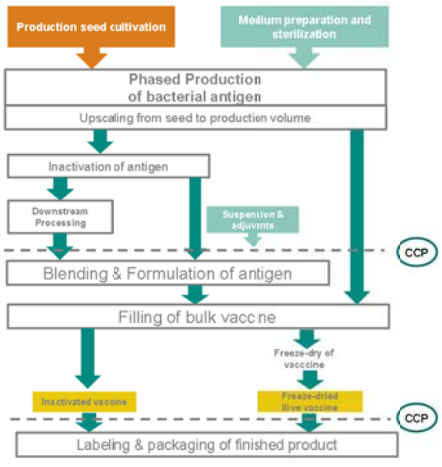
MSD Animal Health

MSD AH NL Operations

MSD AH CoE Quality Operations

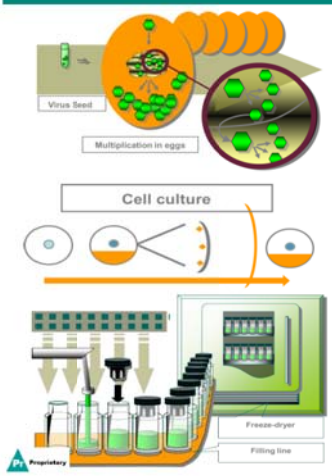
Process overview

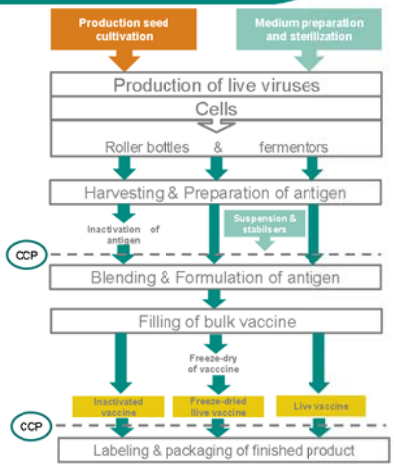
Core Processes – Bacterial Vaccines

Bacterial Processes

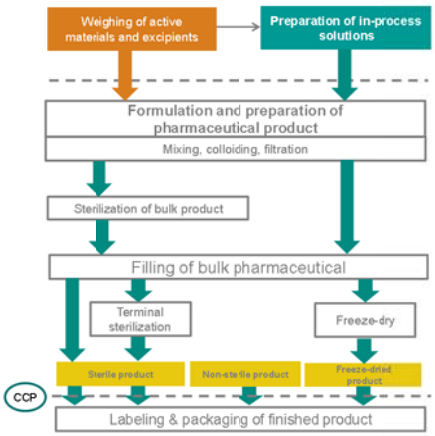
Core Processes – Viral Vaccines





Viral Processes

Core Processes – Pharmaceutical Products



Pharma Processes

THANK YOU

MSD Animal Health

Wageningen Bioveterinary Research

Visit Animal Health Research Institute, Taiwan

October 19th, 2016, Ivo Claassen, PhD

WAGENINGEN UNIVERSITY & RESEARCH

Programme October 19th, 2016

- 9.00 Welcome
- 9.15-10.00 Presentation Wageningen Bioveterinary Research
- 10.00-11.00 Discussion on general vaccine testing and OCABR (Official Control Authority Batch Release)
- 11.00-13.00 Introduction and visit to animal facilities
- 13.00-14.00 Lunch and discussion

WAGENINGEN UNIVERSITY & RESEARCH

Our mission statement

Protecting animal and public health through top level veterinary research.

For quality of life

WAGENINGEN UNIVERSITY & RESEARCH

History

- **1904: RSI**: Rijks Serum Inrichting (Rotterdam)
- **1929: SVOI**: Staats Veeartsenijkundig OnderzoeksInstituut (Amsterdam)
- **1959**: merger RSI and SVOI into **CDI**: Centraal Diergeneeskundig Instituut
- 1972: former SVOI moves to Lelystad
- 1982: former RSI moves to Lelystad
- **1994**: merger with IVVO, IVO and COVP into **ID-DLO**
- 1999: ID-DLO becomes ID-Lelystad, part of Wageningen UR
- **2002**: branch off statutory tasks: **CIDC-Lelystad**
- 2003: merger ID-Lelystad with Praktijkonderzoek Veehouderij and dept. animal sciences into Animal Sciences Group
- **2008**: merger division of contagious diseases ASG and CIDC-Lelystad to **Central Veterinary Institute of Wageningen UR**
- **2016:** name changed into **Wageningen Bioveterinary Research**

WAGENINGEN UNIVERSITY & RESEARCH

Our activities (1)

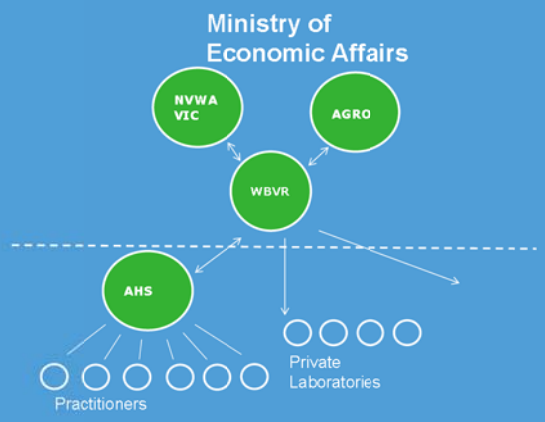
- National reference institute
  - Laboratory diagnosis infectious diseases (NVWA)
  - Supervision on laboratory diagnosis by third parties
  - Development of diagnostic techniques
- International reference laboratory for Campylobacter, Aujeszky's disease, CEM, Q fever

WAGENINGEN UNIVERSITY & RESEARCH

Our activities (2)

- Advice on disease control strategies (Ministry of Economic Affairs)
- Crisis organization disease outbreaks, 24/7 service (NVWA)
- Participation in international research networks
- Contract research for the vet. pharma industry
- Clinical studies
- Knowledge transfer and valorization
- Research according to ISO 9001, ISO 17025

WAGENINGEN UNIVERSITY & RESEARCH



WAGENINGEN
UNIVERSITY & RESEARCH

Our clients

- Dutch ministries (including Ministry of Economic Affairs and Ministry of Public health, Welfare and Sports)
- Industries and providers of service: veterinary pharmaceutical, biotechnology, food, meat
- European Union
- Commodity boards

WAGENINGEN
UNIVERSITY & RESEARCH

Location Houtribweg, Lelystad

WAGENINGEN
UNIVERSITY & RESEARCH

Location Edelhertweg, Lelystad

WAGENINGEN
UNIVERSITY & RESEARCH

Location Runderweg, Lelystad

WAGENINGEN
UNIVERSITY & RESEARCH

Wageningen Wageningen University & Research

- Present at 40 locations in the Netherlands, 1 in China, 1 in Brasil, 1 in Ethiopia
- Faculty and staff: > 6,000
- Turnover: € 710 million (2011)
- Research
  - Top 3 in our domains
  - Top 100 worldwide in university ranking
  - Exploitation and valorisation of research
- Education
  - > 11,000 students

WAGENINGEN
UNIVERSITY & RESEARCH

Organisational structure – **figuur moet nog vervangen worden!**

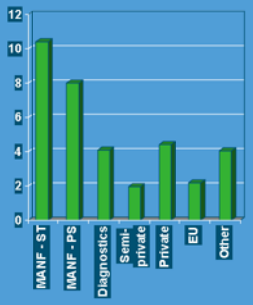
WAGENINGEN UNIVERSITY & RESEARCH

Wageningen Bioveterinary Research, organization

WAGENINGEN UNIVERSITY & RESEARCH

Figures

- Annual Turnover: 37,4 m€
- Strategic Investment: 20%
- Number of employees: 230
- Education of employees
  - Vocational: 33%
  - Higher professional: 36%
  - University: 31%



WAGENINGEN UNIVERSITY & RESEARCH

Facilities

- Laboratories for bacteriology, virology, pathology, fish diseases
- High Containment Unit for high contagious pathogens (BSL 4 veterinary, including BSL 3 human)
- Experimental animal facilities for laboratory animals and farm animals
- Surgery facilities

WAGENINGEN UNIVERSITY & RESEARCH

Core competences

- Diagnoses and crisis organization
- Development of diagnostic tests
- Development of animal models and methods/pathobiology
- Development of models (epidemiology)
- Development of intervention tools (vaccines, therapeutics)
- Pathobiology, animal models and clinical studies

WAGENINGEN UNIVERSITY & RESEARCH

Ambition

- Reinforce position in top 5 of veterinary research institutes in Europe:
  - By focusing on spearheads in research
  - By strategic collaboration with other European research institutes

WAGENINGEN UNIVERSITY & RESEARCH

Research strategy

- Reference laboratory for the public sector: maintain high standard and develop basic expertises
- Supplement with research for 'semi-private' and 'private' sector
- Continue development of market oriented IP portfolio
- Focus and mass: spearhead policy
- Intensify collaboration within Wageningen University & Research and within Knowledge Chain Infectious Diseases (WBVR, FD en GD)
- Strategic collaboration with national and international partners

WAGENINGEN UNIVERSITY & RESEARCH

Collaboration in The Netherlands

- Partners within Wageningen University & Research
- Prominent partner in Knowledge chain veterinary infectious diseases (KID):
  - Faculty of veterinary medicine, University Utrecht
  - Animal Health Service
  - Wageningen Bioveterinary Research
  - ImmunoValley

WAGENINGEN UNIVERSITY & RESEARCH

Research strategy

- Reference laboratory for the public sector: maintain high standard and develop basic expertises
- Solutions for the life stock production sector
- Research for 'semi-private' and 'private' sector
- Continue development of market oriented IP portfolio
- Focus and mass: specific topics
- Intensify collaboration within Knowledge Chain Infectious Diseases (WBVR, Vet.Fac. and AHS)
- Strategic collaboration with national and international partners

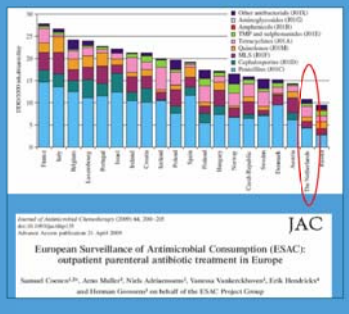
WAGENINGEN UNIVERSITY & RESEARCH

Present problems in livestock farming in NL

- Antibiotic resistance covering endemic disease problems (2011 -20%; 2013 -50%)
- Intensive animal husbandry, discussion about Mega-stables, dairy cattle back in the meadows (welfare, social acceptance , public health)
- Low risk for zoonotic diseases in modern life !?
  - The well organized, modern animal husbandry enabled free status of e.g. TB, Brucellosis, Leptospirosis, Anthrax, Rabies, Avian Influenza etc.
  - The Q fever outbreak created a feeling of unsafety by live- stock farming

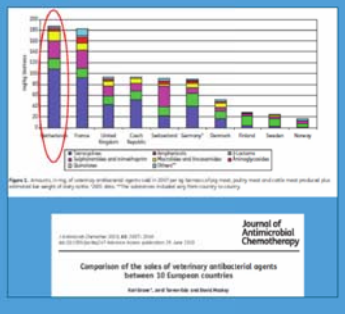
WAGENINGEN UNIVERSITY & RESEARCH

Antibiotic usage in humans and animals in Europe



JAC

European Surveillance of Antimicrobial Consumption (ESAC): outpatient parenteral antibiotic treatment in Europe



Journal of Antimicrobial Chemotherapy

Comparison of the sales of veterinary antibacterial agents between 10 European countries

WAGENINGEN UNIVERSITY & RESEARCH

Antibiotic-free animal husbandry

http://edepot.wur.nl/138451

WAGENINGEN UNIVERSITY & RESEARCH

International collaboration

- Coordinator EU-projects (NoE, IP TB-VAC, many STREP projects)
- Participation in many networks (Venomyc, MED-VET-NET, Neuroprion)
- CoVetLab (5 European reference laboratories)
- EPIZONE
- Working groups ETPGAH
- ERANET
- EFSA panels and working groups
- INRA

WAGENINGEN UNIVERSITY & RESEARCH

Collaboration

- WBVR carries out veterinary research both independently as well as in national and international collaboration
  - Prominent partner in Knowledge chain veterinary Infectious Diseases (KID):
    - Faculty of veterinary medicine, University Utrecht
    - Animal Health Service
    - Wageningen Bioveterinary Research
  - ImmunoValley
  - BVR participates in international networks, e.g.:
    - CoVetLab
    - MED-VET-NET
    - NeuroPrion
    - Venomyc (mycobacteria)

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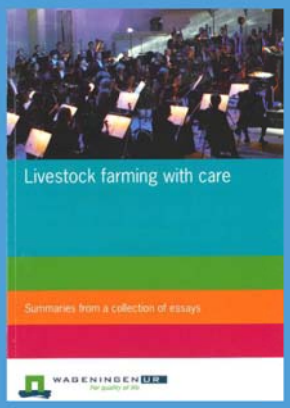
Livestock farming with care



WAGENINGEN UNIVERSITY & RESEARCH

Essay bundle on careful animal husbandry by Wageningen University & Research

About:

- Careful animal husbandry
- Human and veterinairy health
- Respect for animals
- Concern for the environment
- Perspective for farmer and product

- A better future for all of us

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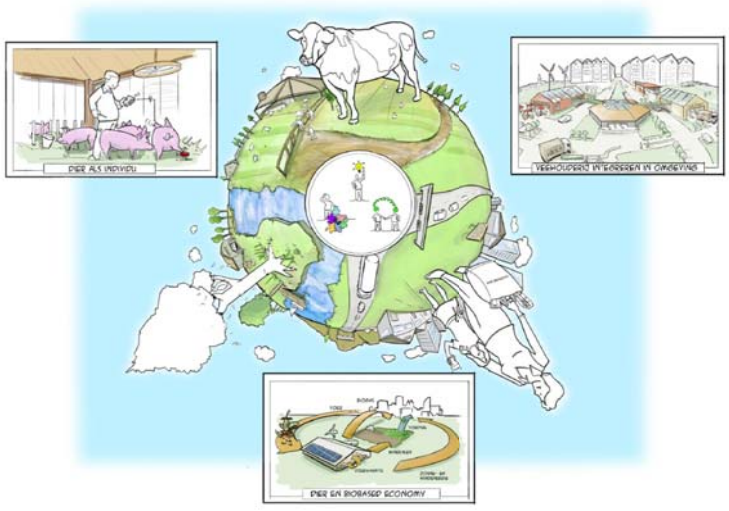
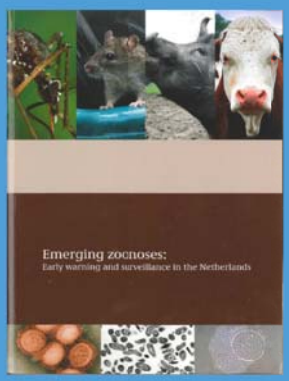


Emerging zoonoses



http://www.rivm.nl/bibliotheek/rapporten/330214002.pdf

WAGENINGEN UNIVERSITY & RESEARCH

Early warning: indicator evaluation for zoonotic infections.

- Experts from the veterinary and human health domain meet each other every month to evaluate signals from the field of zoonotic infectious diseases.
- The core group consists of experts from WBVR, RIVM, Vet. Fac, NVWA and AHS. Other experts can be invited.

WAGENINGEN UNIVERSITY & RESEARCH

Specific research topics

- (Re)emerging infectious diseases and zoonoses like vector borne: APP, BTV, RFVV, CCHF
- Antibiotics resistance
- Host-pathogen interaction/PRRSV
- Gut Health
- Avian Influenza
- Strep. Suis, Q fever
- Epidemiology and risk assessment
- Castellum programme

WAGENINGEN UNIVERSITY & RESEARCH

Virology

- Mammalian Virology
- Avian Virology
- Clinical Studies & Pathobiology

WAGENINGEN UNIVERSITY & RESEARCH

Virology

Focus on various virus diseases
- FMD & Swine Vesicular Disease
- Classical & African Swine Fever
- Exotic viral animal diseases
- Avian Influenza (AI)
- Newcastle Disease (ND)
- Schmallenbergvirus (SBV)

Research on
- Optimizing existing diagnostics
- Development of PCR diagnostics
- Development of (DIVA)-vaccines
- Safety and efficacy of vaccines
- Interaction between host and virus
- Experimental epidemiology
- Data on behalf of risk analysis

WAGENINGEN UNIVERSITY & RESEARCH

Bacteriology & Epidemiology

- General bacteriology and fish diseases
- Antibiotics and zoonoses
- Quantative epidemiology

WAGENINGEN UNIVERSITY & RESEARCH

Diagnostics & Crisis organization

- Crisis organization
- Viral & bacterial diagnostics
- Supervision on private laboratories
- Batch control

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Infection biology

- Vaccine development
- Diagnostics development
- Host
- Pathogen
- Bioinformatica
- Food chain quality and Zoonoses

WAGENINGEN UNIVERSITY & RESEARCH

Animal technology

- **Animal experiments**
  for the researchers of WBVR, ASG and external clients
- Production and/or buying of **qualified experimental animals and derived products**
- Management of the **experimental animal facilities**:Runderweg, Edelhertweg and Houtribweg

WAGENINGEN UNIVERSITY & RESEARCH

Experimental Animal Services: species

- Animal species
  - Poultry, pigs, cattle, sheep, wild life
  - Companion animals
  - Laboratory animals (Rodents)
  - Fish
- Quality
  - Conventional
  - Specified pathogen free (SPF)
  - Designated pathogen free (DPF)
  - Caesarean Derived/Colostrum Deprived (CD/CD)
  - Germ free (GF)

WAGENINGEN UNIVERSITY & RESEARCH

Facilities for large experimental animals

- Conventional and specific housing (Isolators; Bio-exclusion/inclusion)
- High containment facilities (Bio Safety Level 3)
- DM III facilities (GMO)
- Climate accommodation
- Well-equipped Surgery facilities (up to DM II level)

WAGENINGEN UNIVERSITY & RESEARCH

Laboratory facilities/techniques

- Host-pathogen genomics and proteomics
- Biacore, SPR and protein chips platform
- Single domain antibody technologies
- Production of monoclonals
- Recombinant protein expression
- EIA, ELISA, HI, CBR
- PCR
- Blotting
- Molecular engineering, cloning
- Cell culture and virus isolation
- AFLP
- Bacteriophage production laboratory
- Hematological analyses

WAGENINGEN UNIVERSITY & RESEARCH

Crisisorganisation

- 24/7 available
- Crisis scenarios + exercises
- Advice and diagnostics during the crisis
  - 1990: Classical Swine Fever (CSF)
  - 1992: CSF and Swine Vesicular Disease (SVD)
  - 1994: SVD
  - 1997/98: CSF
  - 2001/03: BSE
  - 2001: Foot and Mouth Disease (FMD) and Anthrax
  - 2003: Avian Influenza (AI)
  - 2006: AI, CSF, Bluetongue virus (BTV)
  - 2007-2010: BTV
  - 2009-2010: Q-fever
  - 2011-2012: Schmallenberg virus (SBV)

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Working on approx. 25 virus diseases

- Foot and mouth disease
- Classical Swine Fever
- Rinderpest
- Newcastle disease
- Avian Influenza
- African Swine Fever
- Bluetongue
- Schmallenbergvirus
- African horse sickness
- Bovine leukosis
- Sheep pox and goat pox
- Peste des petits ruminents
- Riftvalley fever
- Vesicular diseases
- Aujeszky's disease
- Rabies
- Fish and shellfish diseases

WAGENINGEN UNIVERSITY & RESEARCH

Working on approx. 70 bacterial /prion diseases

- Salmonella
- Campylobacter
- Tuberculosis
- Brucellosis
- BSE
- Scrapie
- CEM
- Malleus
- American foulbrood
- Psittacosis
- Q fever
- Botulism
- Contagious bovine pleuropneumonia
- Leptospirosis
- Fish and shellfish diseases
- Wild life mortality
- Antibiotics resistance

WAGENINGEN UNIVERSITY & RESEARCH

Contract research for industry

- Quality standards: NEN-EN-ISO 9001:2008 and ISO 9001, NEN-EN-ISO/IEC 17025:2005
- Independent and confidential
- Research & Development in house
- Pre-clinical and clinical registration studies
  - Biologicals
  - Pharmaceuticals
  - Experimental animal services
- Animal Models
- Batch controls

WAGENINGEN UNIVERSITY & RESEARCH

Securing statutory research tasks (WO-tasks)

- WO-tasks as separate program in BVR
- WOT program leaders in line management in order to guarantee priorities and performance during crises
- Positioning employees in columns (1,2 or 3)
- Check on privately funded research for potential conflict of interest
- Annual audit specifically on statutory tasks

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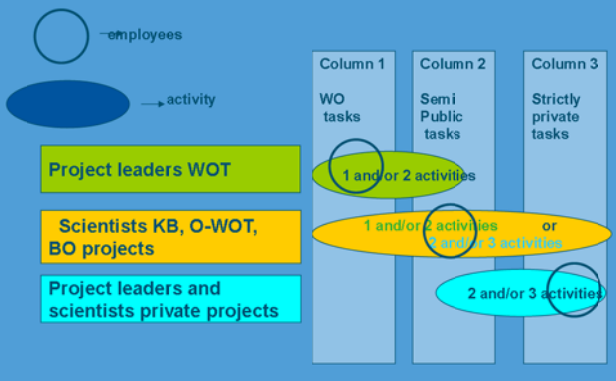
Separation WOT - private in backoffice



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Thank you for your attention

WAGENINGEN UNIVERSITY & RESEARCH

http://www.cvi.wur.nl/uk

Wageningen Bioveterinary Research (WBVR)

19 October 2016

Animal Drugs Inspection

Branch Animal Health Research Institute

Taiwan

Henk Sloetjes

Department for Animal Technology

WAGENINGEN UNIVERSITY & RESEARCH

Wageningen Bioveterinary Research

WAGENINGEN UNIVERSITY & RESEARCH

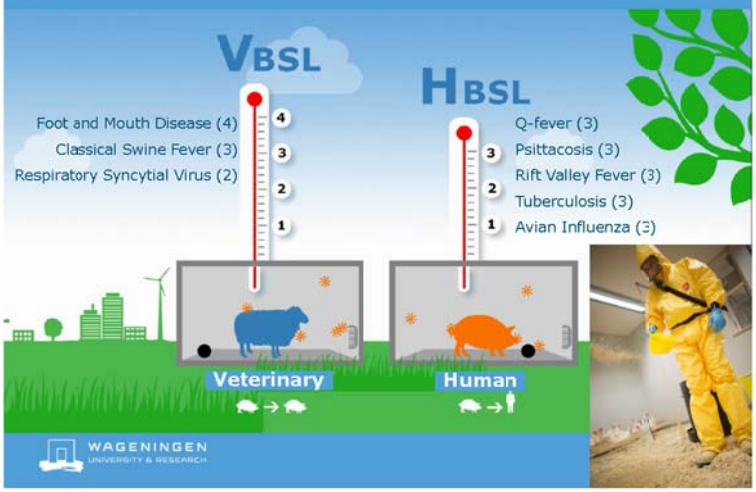
WBVR: What we have....

- Laboratories
  - Classical virology / bacteriology
  - Molecular biology, incl. next generation sequencing, microarrays (gene expression)
  - Pathology
  - Immunology
  - BSL-III

- Animal facilities
  - Farm & laboratory animals
  - Up to human BSL-III & veterinary BSL-IV
  - GMOs (up to DM-III)

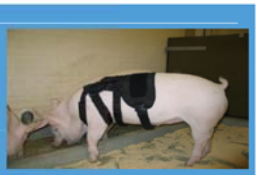
WAGENINGEN UNIVERSITY & RESEARCH

Facilitating research at all Biosafety Levels



WAGENINGEN UNIVERSITY & RESEARCH

Department for Animal Technology



- Planning, organization and realization of animal experiments for the researchers of CVI, ASG and external clients
- Production and/or buying of qualified experimental animals and derived products
- Management of the experimental animal facilities: Runderweg and Houtribweg

WAGENINGEN UNIVERSITY & RESEARCH

Experimental Animal Services: species

- Animal species
  - Poultry, pigs, cattle, sheep
  - Companion animals
  - Laboratory animals (Rodents)
  - Lama, wild life

- Quality
  - Conventional
  - Specified pathogen free (SPF)
  - Designated pathogen free (DPF)
  - Cecarean Derived/Colostrum Deprived (CD/CD)
  - Germ free (GF)

WAGENINGEN UNIVERSITY & RESEARCH

Wageningen Bioveterinary Research: Department of Animal Technology (DB)

Location Runderweg (RDW)

SPF, CD-CD, DPF, BSL1

Location Houtribweg (HRW)

BSL 2, h+vBSL3, vBSL 4

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DB: Experimental Animal Facilities 2016

Location:	RDW	HRW (HCU)
	SPF/CD	
	BSL 1	
		BSL 2(DM 2)
		BSL 3(DM 3)
		hBSL 3+
		vBSL 4

Total: 2.900 m² *nett* animal-room(-space)

10.000 m² *gross* surface (107.500 ft²)

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Runderweg Animal Facilities

- SPF/CD-CD
- Conventional
- Bio Safety Level 1
- SPF dog breeding colony
- Operation/pathology facilities

All facilities are multipurpose!

Suitable for all species!

Animal Rooms:

35 m² to 340m²

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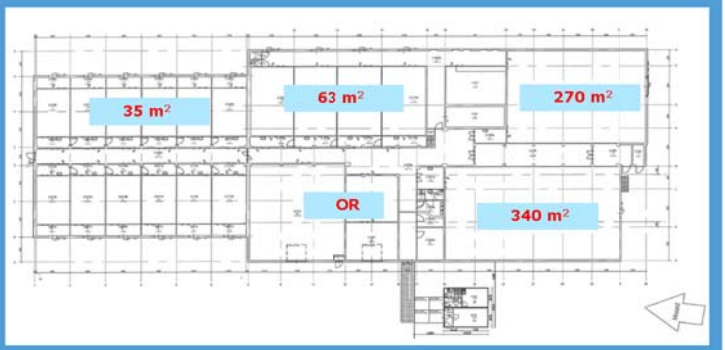
Floorplan Runderweg 160



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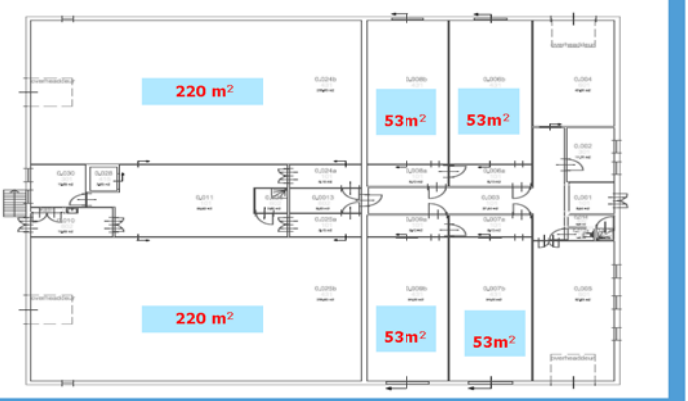
Floorplan Runderweg 161



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WBVR High Containment Unit (HCU)

- 20 different laboratories
- 3500 m2 net total lab space
- Completely BSL4 veterinary in which:
  - BSL3 Human
  - Isotope, PCR, GMO

- 16 MP Animal rooms BSL 2
- 20 MP Animal rooms vBSL4
- 10 MP Animal rooms hBSL3
- 15 m² < > 250 m²
- Total >1700 m² (NFS)

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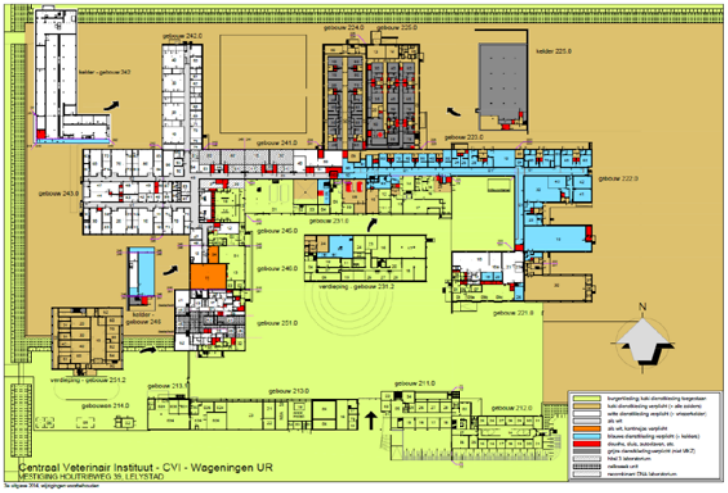

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Risk groups of biological agents

Biological agents are classified for humans and animals into four risk groups, according to their level of risk for an infection and profylaxe or treatment.

Risk group	Pathogenicity	Profylaxe / treatment for humans	Examples	BioSafety Level	Research CVI Vet.	Hum.
1	-	NA	Lactobacilli	BSL 1	+	+
2	+	+	*S. aureus*	BSL 2	+	+
3	++	+	AI	BSL 3	+	+
4(v)	+++	-	MKZ	BSL 4	+	-
4(h)	+++	-	Ebola	BSL 4	-	-

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Humaan BioSafety Level 3+

Decontamination:

- Air: HEPA Filters
- Liquid: killtank(chemical) ETS (thermically)
- Vast: autoclaaf (thermically)
- Cadavers: digester

- Personel: - PPE
  - Quarantaine

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hBSL3 Personal Protection Equipment

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Internal Quarantine

entrance registration

fingervein

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shower/airlock/door-interlocking

- 3 min. shower

5 min. airlock

60x/h, (validated) complete air-chainge

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High Pathogene Avium Infuenza (HPAI) in chicken

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Q fever (coxiella burnettii) in sheep

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HBSL3 autopsy-room

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closed transport-circuit

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High level of animal welfare "High Animal welfare in High Containment"

- CVI complies with the legal requirements for animal welfare for all animal species, at acceptable costs, acceptable risks and limited additional work.
- The level of animal welfare is achieved thrcugh standardised animal units and management.
- Taking good care of animal welfare creates public support.

WAGENINGEN UNIVERSITY & RESEARCH

Development 2015 → 2016 "digitisation"

- 2015: Validation and Implementation E-Book→ go life!

- Q2 2016: E-planning
- Q3 2016: E- cost-calculation

- 2016-2017: telemetry

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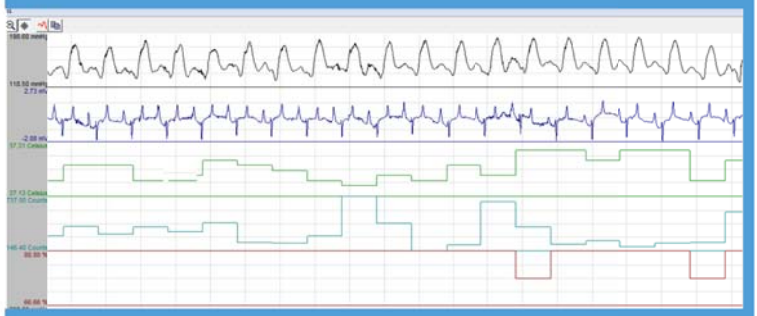
Output: Physiological parameters
ECG, blood-pressure, temperature, activity

Continuous simultaneous measurement of 12 animals



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CENTRAL VETERINARY INSTITUTE WAGENINGEN UR

Our product.....

- Raw data
- Digital reports (interim callable)

iVENTION make IT work for you

Registered by the animal technicians in a custom made software application

WAGENINGEN UNIVERSITY & RESEARCH

BioChek

BIOCHEK, SMART VETERINARY DIAGNOSTICS

BioChek Animal Health Monitoring System

BioChek's Mission

Provide our customers with an accurate, reliable and easy-to-use animal health monitoring system in order to improve the health, productivity, and welfare of livestock

BioChek

BioChek Milestones in history

- Founded in 1997
- Merged with Chromotech in 2003
- 2005 ISO-9001
- 2011 USDA
- 2016 >50 employees world wide

BioChek

About Biochek

Smart Veterinary Diagnostics

- Animal Health and Food Safety
- We provide an Animal Health Monitoring system
- A good monitoring system allows for:
  - Identifying trends in the immune status allowing for corrective action
  - Identifying presence of unwanted organisms

BioChek

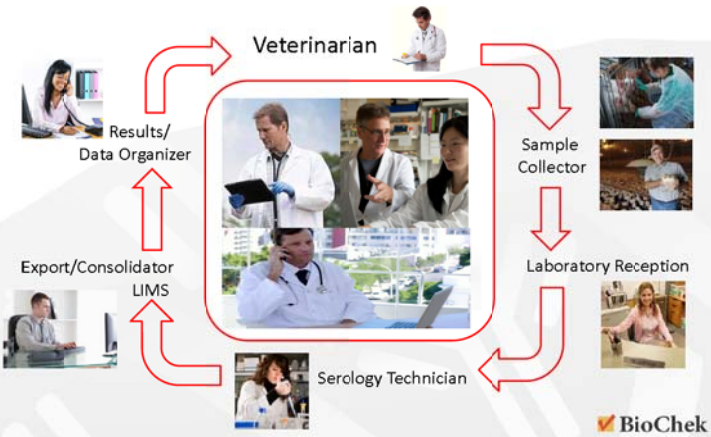
BioChek Monitoring System

The BioChek Animal Health Monitoring system consists of:

- Diagnostic test kits (ELISA & qPCR)
- Software allowing for 24/7 data access anywhere
- Systems to help customers generate reproducible and accurate test results:
  - Reference controls
  - BioChek ELISA Assay Robot (B.E.A.R.)
  - Technical support

BioChek

Animal Health Monitoring System



BioChek

BioChek Offices & Representatives

BioChek

Customers

- Veterinary practise laboratories
- Independent laboratories
- Primary breeders
- Integrators
- Vaccine companies
- SPF egg producers

BioChek

Customers

BioChek

What's so special about BioChek?

- Comprehensive product range
- Strong technical support
- Reference controls
- Product availability
- Easy to use software with 24/7 access to trend reports and results

BioChek

BioChek ELISA Assay Robot

Equipment

- Runs all BioChek kits
- Easy to operate
- Fully automated: load and walk away
- Runs up to 6 plates a day

B.E.A.R.
POWERED BY BIOCHEK

BioChek

BioChek
BIOCHEK, SMART VETERINARY DIAGNOSTICS

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E-mail: *timgoode@biochek.com*

COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN

C B G
M E B

MEDICINES
EVALUATION
BOARD

Bureau Diergeneesmiddelen

Veterinary Medicinal products Unit

- History
- General information
- Registration of veterinary medicines
  - Identical processes as for Human Medicines
- The world of veterinary medicines
  - Differences
  - Examples
- Conclusions

History

- Registration veterinary medicines since 1986
- Ministry of Economic Affairs
- Since 1 March 2005 part of aCBG-MEB
- Veterinary Medicinal Product Unit (VMPu)

General information VMPu

- Part of Agency MEB but different legal construction
- Minister of Economic Affairs is responsible
- Ministry of Economic Affairs is contract party
- NL-policy by Ministry of Economic Affairs
- BD project-organisation

VMPu

- Marketing authorisation of veterinary medicines
- Pharmacovigilance
- Feed additives (herbals)
- Homeopatic products
- Authorisation manufacturing, import, whosale & retailtrade (inclusive inspection) ;
- Exportcertification of VMP
- Support of policy makers (inclusive EU)
- Advising/Informing

Indicators VMP

- Number of registrations (10-10-2016) 2604
- New registrations/year 100-125
- Scientific assessments 200-300
- Variations 500-600
- Licenses and Certificates 2500
- Batch release vaccines 1310

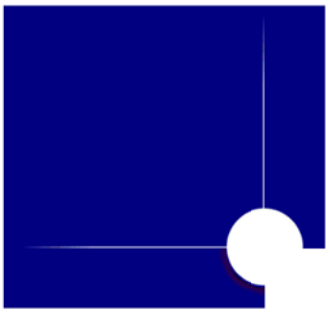
- Turnover BD ca 5.0 million €.

RMS for MRP/DCP 2015

AT	BE	CZ	DE	ES	FR	HU	IE	IT	NL	UK
1	5	4	6	22	20	5	22	2	8	73

VMPu:

- 3 senior RPL (CVMP- en CMDv-member)
- 12 Registration Project Leaders
- 3 clinical assessors
- 7 Registration Project Officers
- 1 coördinator pharmacovigilance
- 1 coördinator licensing
- 2 admin. licensing
- 1 head



COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

CBG MEB

MEDICINES EVALUATION BOARD

Medicines Evaluation Board Agency – Veterinary Medicinal Products Unit

Assessment Veterinary Medicinal Products NL

Agenda

- Marketing authorisation Procedures
- Assessment
- Potential Serious Risk (PSR)
- Routing of assessment
- Official Batch Protocol Review (OBPR)and Official Control Authority Batch Release (OCABR) for IVMP

Marketing authorisation procedure

National procedure

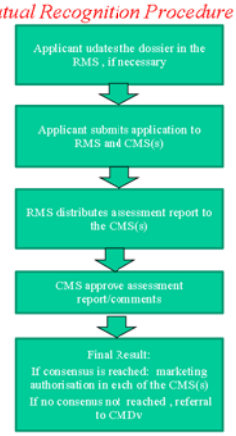
Mutual Recognition Procedure

Decentralised Procedure

Centralised procedure

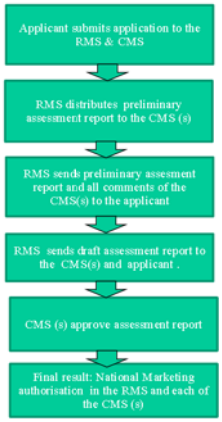
Marketing authorisation procedure

Mutual Recognition Procedure (MRP)



Marketing authorisation procedures

Decentralised Procedure



Marketing authorisation procedures

Centralised procedure

Applicant applies to the EMA for marketing authorisation and finally receives one European approval which is valid in countries of the community, as well as Norway, Iceland and Liechtenstein. The centralised procedure

Assessment

- Quality
- Efficacy - bioequivalence
- Animal safety
- Consumer safety
- User safety
- Environment

EMA - Scientific guidelines

Focus NL on:

Antibiotic resistance, consumer safety & environment

Potential Serious Risk (PSR)

Consumer:

*PSR if withdrawal period * does not provide sufficient degree of assurance.*

*Withdrawal period = period between last administration of the VMP and moment of slaughter.

User:

PSR exists if precautionary measures are not sufficient to reduce the risk to an acceptable level.

Potential Serious Risk (PSR)

Animal:

Efficacy – not sufficiently proven/ not bioeq.

Safety – risk unacceptable or not adequately addressed in labelling

Quality – if production and control does not guarantee that major deficiency will not occur

Potential Serious Risk (PSR)

Environment:

2.3. **Potential serious risk for the environment**

Applicants are required to submit a complete report which concludes with an Environmental Impact Assessment (EIA) based on the characteristics of the product, its potential environmental exposure, environmental fate and effects as well as risk management strategies as appropriate. The report should take into account the pattern of use, the administration of the product, the excretion of active substance and major active metabolites as well as the disposal of the product.

Major risk for one or more compartments (e.g. water, air, soil), which can not be mitigated

Routing of assessment - MEB

Regulatory Project Leader (RPL) presents procedure at time of Validation, Day 100/145/pre-CMDv in

TECHSEC – meeting (weekly)

All RPLs, CVMP member, CMDv member, Head of Unit & some internal assessors

Routing of assessment - MEB

Regulatory Project Leader (RPL) presents procedure at time of Validation, Day 100/145/pre-CMDv in

TECHSEC – meeting (weekly)

All RPLs, CVMP member, CMDv member, Head of Unit & some internal assessors

Consistency in Assessment/SPC text

Routing of assessment - Second Opinion

PSR → Scientific Board **Second Opinion**

Artikel 2.1 Commissie registratie diergeneesmiddelen

1. Er is een Commissie registratie diergeneesmiddelen.
2. De Commissie adviseert, desgevraagd, de minister over vergunningen voor het in de handel brengen van een diergeneesmiddel.
3. De minister benoemt en ontslaat de leden van de Commissie.
4. De Commissie bestaat uit zeven leden en vergadert met minimaal vijf leden.

7 Members (external/independent) & secretariat MEB Agency

MEB Agency Introduction Issue & Minutes
- Head of Unit & Head of Agency
- Regulatory Project Leader
- CVMP member and alternate
- CMDv member

Routing of assessment - Second Opinion

Scientific Board's **ADVICE (Pos or Neg)**
to
Chief Veterinary Officer - CVO

CVO receives:
1. Initial AR - Appointed Institutes
2. Summary Discussion & Advice - Scientific Board
3. Remarks - MEB Agency
   - Procedural aspects
   - Overview similar decisions in past
   - Outcome of previous referrals

Routing of assessment - final decision

DECISION of Chief Veterinary Officer

or

Referral

(= further discussion and finally European Commission Decision)

OBPR/ OCABR for IVMP

Background:

EU Directive 2001/82/EC currently under revision

Directive regulates OBPR (art.81) and OCABR (art.82) for IVMP

OBPR/ OCABR for IVMP

Special aspects of IVMP

- *use of biological systems for production and testing*
- *complex manufacturing processes*
- *complex control methods*
- *control of potential viral safety risk*
- *contamination by (un)know infectious agents*
- *administration to large number of healthy animals*
- *government-mandated/supported vaccination/eradication programmes*
- *complex products require official product testing*
- *EDQM-OBPR/OCABR*

Thank you for your attention !