IRISH MEDICINES BOARD

RESIDUAL SOLVENTS CONTROLS

E.U. PERSPECTIVE

18th Jan 2007

PDA /USP Joint Meeting

North Bethesda Marriott Hotel & Conference Center

North Bethesda, Maryland

IRISH MEDICINES BOARD

RESIDUAL SOLVENTS CONTROLS

E.U. PERSPECTIVE

18th Jan 2007

PDA /USP Joint Meeting

North Bethesda Marriott Hotel & Conference Center

North Bethesda, Maryland

IRISH MEDICINES BOARD

RESIDUAL SOLVENTS CONTROLS

E.U. PERSPECTIVE

18th Jan 2007

PDA /USP Joint Meeting

North Bethesda Marriott Hotel & Conference Center

North Bethesda, Maryland

OVERVIEW

- Introduction – regulation of medicines
- Regulatory guidance
- New vs. Established Drugs
- Structure and role of European Pharmacopoeia
- RS and the Pharmacopoeia

IRISH MEDICINES BOARD

INTRODUCTION Regulation of Medicines

- Regulatory Platforms
  - Quality
  - Safety
  - Efficacy
- Quality by product and process design
- Maintenance of quality standards throughout lifetime
- Application of GMP, GXP
- Human and animal medicines have similar standards.

IRISH MEDICINES BOARD

LEGISLATION SYSTEM

- European Legislation System
  - Directives, Regulations, Opinions, Positions etc.
  - Generally binding on Member States

- National Legislation
  - Primary Legislation
  - Secondary Legislation
  - Guidelines, administrative provisions and codes of practice

IRISH MEDICINES BOARD

CODIFIED DIRECTIVE 2001

- 2001/83/EC – human medicines
- 2001/82/EC – vet medicines
- Combines all relevant current directives into one document in each case for human and animal medicines
- Safeguard public health by regulation of medicines
- Not hinder development/trade
- Foster single market
- Define medicinal product
- Regulation of marketing, manufacture and distribution.
- Labelling, promotion and advertising
- Pharmacovigilance

IRISH MEDICINES BOARD

REVISION OF EU LEGISLATION

- Regulation 726/2004/EC – replaces 2309/93 – EMEA, centralised procedure
- Directive 2004/27/EC – amends 2001/83/EC
- Directive 2004/28/EC – amends 2001/82/EC
- Directive 2004/23/EC – Tissues and cells Directive (April 2006)
- Directive 2003/94/EC – GMP for MP's and IMP's (April 2004)
- Directive 2004/24/EC – Registration of Herbals (THM's) for human use
- Implementation deadline 31/10/05

IRISH MEDICINES BOARD

Quality Actors in the EU

- EMEA/CHMP/CVMP - National Agencies
- CHMP Working parties
  - Quality Working Party (+ CVMP)
  - Biotech Working Party
  - Inspector's Working Party
- European Directorate of Quality of Medicines (EDQM):
  - European Pharmacopoeia (national pharmacopoieas)
  - OMCL network
- Industry: pharmaceutical / chemical
- Wholesalers
- Pharmacies
- Physicians

IRISH MEDICINES BOARD

ICH TOPIC Q3C

- Solvents frequently present in pharmaceuticals
- Necessity to use solvents in synthetic processes
- Need to restrict solvents in drug substances and products
- All solvents are impurities – no therapeutic benefit
- Recognition of the need for harmonised guidance.
- Inclusion in the ICH process – early 90's
- Q3C Step 4 guidance July 1997 adopted CPMP September 1997

IRISH MEDICINES BOARD

ICH Q3C GUIDELINE FOR RESIDUAL SOLVENTS

- Introduction
- Scope – new drug substances and product
- General Principles – risk based
- Limits of Residual solvents and two options on how to calculate permitted daily exposures
- Classification of solvents

IRISH MEDICINES BOARD

Q3C - INTRODUCTION

- **Objective:**
  - Guidance for acceptable quantities of solvents
  - Recommendation for use of safer solvents
- **Definition**
  - Residual Solvents are volatile organic solvents used or produced in the manufacture of DS/DP or Excipients.
- **Classification of Solvents –**

  Class 1,2,3

IRISH MEDICINES BOARD

Q3C – SOLVENT CLASSIFICATIONS

- Class 1: Solvents to be avoided;e.g, benzene, carbon tetrachloride

- Class 2: Solvents to be limited; e.g, acetonitrile, chloroform, dichloromethane, hexane, methanol, toluene, 1,4-dioxane, THF.

- Class 3: Low toxic potential: e.g, acetic acid, acetone, heptane, ethanol

IRISH MEDICINES BOARD

USE AND TESTING FOR SOLVENTS

- Use preferably Class 3 Solvents

- Monitor the amounts of solvents either
  - by testing the DP directly or
  - by testing each component in the DP and by totalling these amounts to calculate total amount in DP.

IRISH MEDICINES BOARD

NEW AND ESTABLISHED ACTIVE SUBSTANCES

- ICH Guidance developed for new products containing new active substances (AS)
- Excluded - new products containing established AS
  - existing marketed products
  - products under clinical development (IMP's)
- However Q3C is based on a safety evaluation
- Illogical to exclude established substances

IRISH MEDICINES BOARD

ESTABLISHED ACTIVE SUBSTANCES

- Guideline (CPMP/ICH/283/95) therefore made applicable to all marketing authorisation applications with effect from March 1988
- Active substances, excipients and new products containing them
- Extended to all existing marketed products within a 2 year time frame (July 2000)
- Useful also for products in clinical study – safety based.

IRISH MEDICINES BOARD

CLASS 1 AND CLASS 2 Solvents in Active Substances

- Annex to ICH guideline Q3C – March 1998
- " " VICH " GL18 – June 2001
- Guidelines are in use and clarification proposed to deal with problems in practice
- "Class 1 Solvents should not be used because of safety concerns"
- Where unavoidable – strict limits to be applied
- Solvent could also be used as a starting material, or could be present as a by-product or impurity

IRISH MEDICINES BOARD

Class 1 solvent as starting materials

- Examples benzene; 1,2-dichloroethane
- May be unavoidable – benzene ring is part of structure
- Early steps in the synthetic route?
- Control at appropriate intermediate downstream or at final active substance level
- ICH limits apply

IRISH MEDICINES BOARD

Class 1 Solvent as an impurity

- Benzene maybe a reaction by-product
- Benzene always present in toluene
- Can limit the toluene content in the active substance to ensure benzene remains below ICH limit
- Demonstrate that the Class 1 solvent is nmt >30% specified limit in suitable intermediate – validated methods
- Data for 6 consecutive pilot or 3 industrial scale batches of intermediate or final active in support
- Otherwise test each batch of active

IRISH MEDICINES BOARD

Class 2 Solvents

- Limits for ICH apply to the final active substance
- Last step – test the final active substance
- Use prior to last step – show nmt 10% ICH limit present in final active or suitable intermediate
- Batch data from 6 pilot or 3 consecutive industrial batches demonstrating compliance to suppest absence of routine test.

IRISH MEDICINES BOARD

Solvents in the manufacture of finished products

- Organic solvents may be unavoidable in DP manufacture – eg granulation, coating of tablets
- Class 1 solvents should not be used
- Class 3 solvents should be used where possible
- Include test for solvent residue in finished product
- Class 3 solvents can be limited to 0.5% by LOD
- For Class 3 solvents > 0.5%, or if Class 2 solvents used – a specific (chromatographic) technique to be used

IRISH MEDICINES BOARD

Questions?

Thank you for your attention.

IRISH MEDICINES BOARD