Diapharm

we present

Jun 25th, 2015
CPhI, ICSE & P-MEC China Innovation and Development Forum
Ralf Sibbing, General Manager / Partner

The European Pharma Market - An Overview
Hurdles and Opportunities of upcoming changes

Agenda

- **European Pharma Market – Introduction and figures**
- **European Market – Size and diversification**
- **(Upcoming) changes in Clinical and Pharmacovigilance**
- **Upcoming changes in Regulatory Affairs**
- **Upcoming changes in Quality**

Diapharm

European (Union) market

- 28 member states developed a free market
- 24 official languages
- Capital: Brussels
- approx. 507 Mio. combined population (2014 estimate)
- GDP about 19.045 trillion US-$ (2015 estimate)

Diapharm

The Global Pharmaceutical Market 2013

Development of the global pharmaceutical market

	2009	2010	2011	2012	2013
Total market (billion Euros)*	610.1	654.7	709.0	703.2	720.0
Total market (billion US-Dollars)	830.6	891.3	965.2	957.3	980.1
Change compared to previous year (in %)		7.3	8.3	- 0.8	2.4

* The Euro values are based on a recalculation of the market data of the base values in US-Dollars (Exchange rate: US-Dollars in Euros = 1.361 : 1).

Source: Illustration of the BPI based on data of IMS World Review Review 2014.

Europe: 189.6 billion Euros (+ 5.6 %)

Diapharm

European Pharma Market 2013

Pharmaceutical markets of the EU-15

EU member state	Turnover* for 2013 (Million USD)	Growth*** to LCD 2013 (%)	Turnover* for 2013 (Million Euros)****
Germany**	45,828	5	33,664
France**	37,156	-2	27,294
Italy**	27,930	3	20,517
Great Britain**	21,635	17	15,893
Spain**	20,741	1	15,236
Belgium**	6,122	0	4,497
Sweden**	4,464	0	3,279
Greece	4,460	-10	3,276
Austria**	4,261	2	3,130
The Netherlands	3,868	-3	3,086
Portugal	2,691	-1	2,841
Denmark**	2,691	2	1,977
Finland**	2,653	-3	1,949
Ireland**	2,397	0	1,761
Luxembourg	237	0,5	174
Total	188,644	2.98*****	138,573

* Turnovers from the markets observed, plus estimation of partial markets not observed, result in the total turnover of a member state at manufacturer price.

** Pharmacy market and hospital market data were available for these markets.

*** LCD: Local currency dollar – currency fluctuations in each country are not considered, so the growth rate is comparable across countries.

**** The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1 : 1.361).

***** The total growth in LCD 2012 of 2.98 % is a weighted value (unweighted: 0.5 %).

Source: Illustration of the BPI based on data of IMS Health World Review 2014.

Diapharm

European Pharma Market

- Heterogeneous with regards to market size and market development
- Pharmaceutical pricing and reimbursement are regulated in different ways in different countries
- A common feature of these markets is an increasing competition in the generics sector

Diapharm

European Pharma Market Prognosis

Market prognosis using constant exchange rates, growth in %, manufacturer price.

Europe	2012 – 2017
EU top five countries	1.9 %
EU member states	1.8 %
Non-EU countries	2.9 %
Global market	5.1 %

Source: Illustration of the BPI based on data of IMS Market Prognosis Global 2014.

Diapharm

European Pharma Legislation

- The pharmaceutical industry is one of the most highly regulated industries in the world across all of its activities.

- The European Union (EU) and its Member States are responsible for an increasingly complex web of legislation and regulation, which seeks to protect public health whilst establishing a common market for pharmaceuticals.

Diapharm

European Pharma Legislation

EU Legislation and regulation covers the full lifecycle of pharmaceutical products, including:

- marketing authorisation,
- clinical trials,
- competition law and intellectual property rights,
- trade,
- post-authorisation safety (pharmacovigilance),
- and advertising.

Diapharm

(Upcoming) Changes in Clinical Affairs – New EU clinical trials regulation

REGULATION (EU) No 536/2014* (in force 2016)

New procedure for clinical trials application:

- 😀 Only one application for all included countries, covering authorities of concerned member states and ethical committees
- 😟 Procedure very complicated: only via online gateway, still to be constructed (until 2016)

*REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Diapharm

(Upcoming) Changes in Clinical Affairs – New EU clinical trials regulation

New transparency regulation for publication of clinical study reports; further regulations planned for publication of complete study master files

- 😀 Higher transparency of clinical study results, including negative results
- 😟 Risk of disclosure of confidential data to competitors

Higher standards for informed consent of children and adolescents

- 😀 Higher ethical standard
- 😟 Increased study duration due to slower enclosure rates

Diapharm

Changes in Pharmacovigilance

Legal Background

EU drug safety requirements have dramatically increased over the last 5 years due to several legislative acts:

- Directive 2010/84/EU [amending Directive 2001/83/EC]
- Regulation (EU) No 1235/2010 [amending Regulation (EC) No. 726/2004]
- Commission Implementing Regulation No 520/2012 of 19 June 2012

Diapharm

Changes in Pharmacovigilance 2010 - 2012

Good Pharmacovigilance Practice (GVP)

The GVP provides guidance to facilitate the performance of pharmacovigilance in accordance with the legislation:

Good pharmacovigilance practices*

Key Players in EU Pharmacovigilance

- European Medicines Agency (EMA)
- National Competent Authorities (NCA) in the EU Member States
- Marketing Authorisation Holders

*http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Diapharm

Changes in Pharmacovigilance – major steps

- **EU/Local-QPPV** - notification of appropriately qualified responsible persons to EMA [EU-QPPV] and NCA [Local QPPVs]

- **PV Quality System** - implementation of a quality system / written procedures appropriately covering all PV-related processes

- **Electronic Reporting** - electronic submission of adverse drug reaction [ADRs] reports to EMA and NCAs within fixed timelines [15/90 day timelines]

- **PV Literature Search** - weekly worldwide and local literature monitoring

Diapharm

Changes in Pharmacovigilance- continued

- **Benefit-Risk-Analysis** - continuous benefit-risk analysis and risk signal detection based on spontaneous ADR reports , worldwide literature monitoring and other sources of information

- **RMPs/PSURs** - preparation and submission of pharmacovigilance related documents/reports during Marketing Authorization procedures [risk management plans] and product lifecycle [periodic safety update reports]

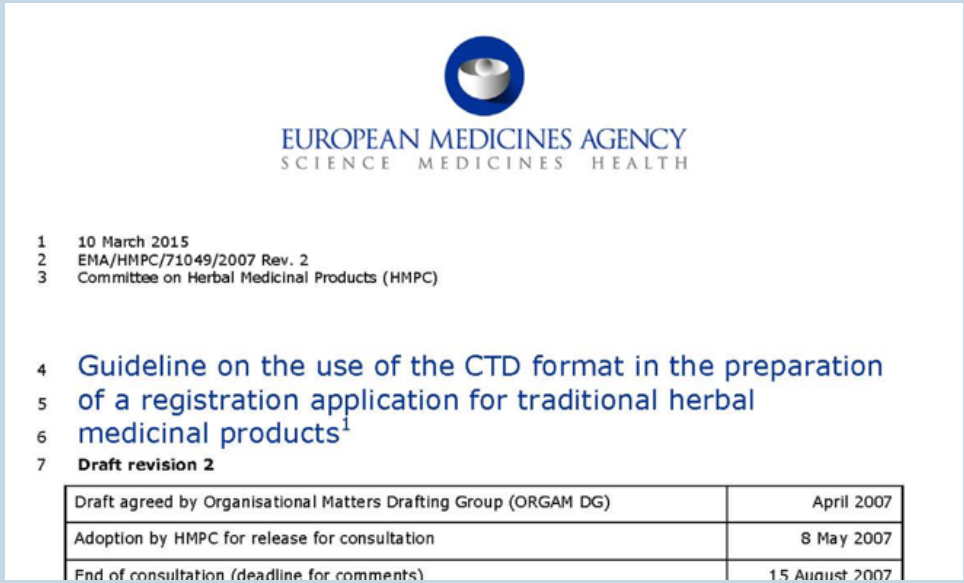
- **xEVMPD database** - submisssion and continuous update of product specific data to the EMA medicinal product database (xEVMPD database)

Diapharm

(Upcoming) Changes in Regulatory Affairs - Herbal Medicinal Products

Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products (EMA/HMPC/71049/2007 Rev. 2)

- Still in draft status, comments until July 15th, 2015
- Guideline reflecting special situation of herbal preparartions
- Appendix 1 giving a sample module of part 3.2 for Valerian root



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 10 March 2015
2 EMA/HMPC/71049/2007 Rev. 2
3 Committee on Herbal Medicinal Products (HMPC)

4 Guideline on the use of the CTD format in the preparation
5 of a registration application for traditional herbal
6 medicinal products[1]
7 **Draft revision 2**

Draft agreed by Organisational Matters Drafting Group (ORGAM DG)	April 2007
Adoption by HMPC for release for consultation	8 May 2007
End of consultation (deadline for comments)	15 August 2007

Diapharm

(Upcoming) Changes in Regulatory Affairs
eCTD-Roadmap

eCTD (electronic Common Technical Document):

• The electronic Submission (eSubmission) Roadmap aims at establishing secure, consistent and efficient electronic submission processes for medicinal products for human and veterinary use across the European Medicines Regulatory Network (ERMN or "the Network"). (vom CMDh)

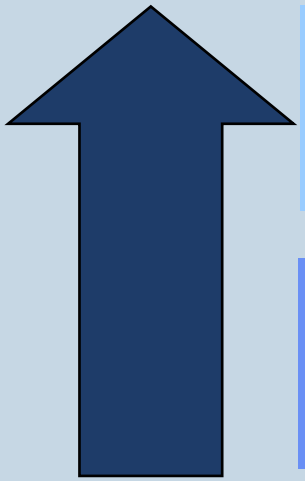
• The eSubmission Roadmap is a high level strategic plan for business and technology change, typically operating across multiple disciplines over several years. (vom CMDh)

➔ eCTD 4.0 obligatory from end of 2016

Diapharm

Changes in Quality - Strengthening of GMP requirements

GMP = Give Me Paper?



Withdrawal & Supension of GMP / COS certificates

Announce / Unannouced Official Inspection

Diapharm

Strengthening of GMP requirement
MHRA - Data Integrity definitions and guidance

- **MHRA published "Good manufacturing practice: data integrity definitions and guidance on January 23, 2015。**

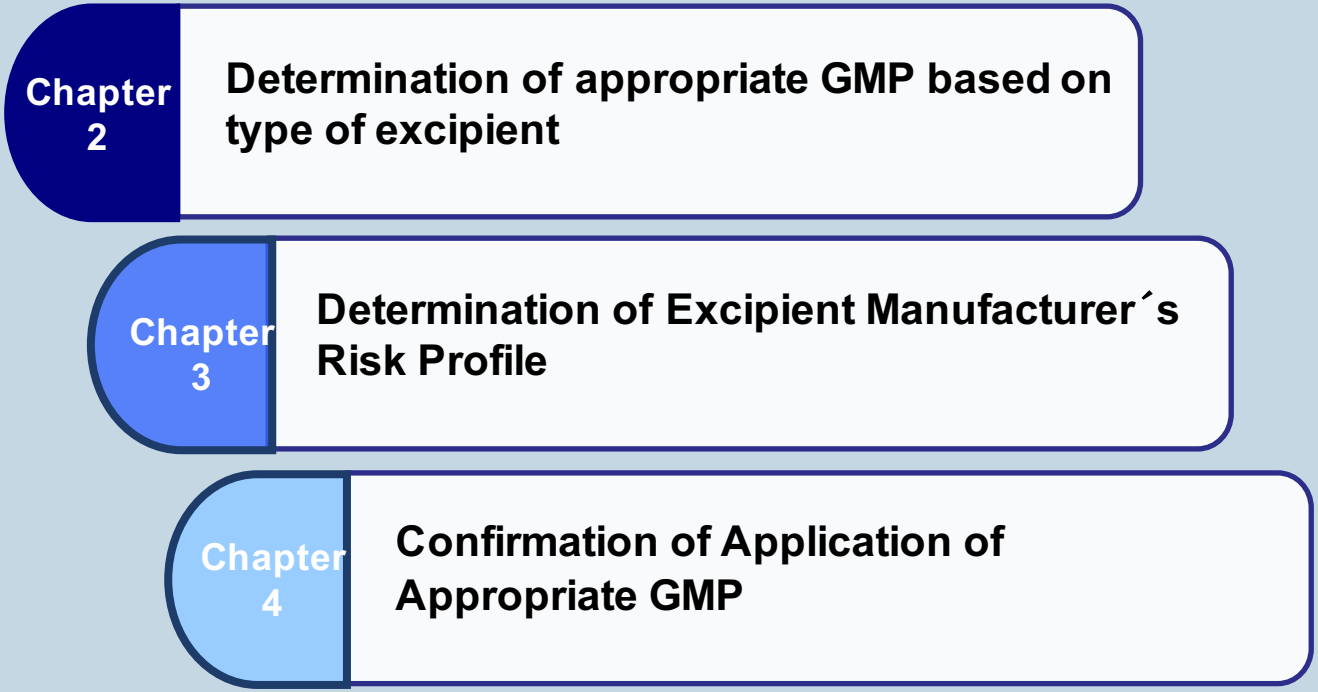
- **"Establishing data criticality and inherent integrity risk"**
- **"Designing systems to assure data quality and integrity"**

Data	*Raw Data*	*Meta Data*	*Data Integrity*
Data Governance	*Data Lifecycle*	*Primary Record*	*Original Record*
True Record	*Computer System*	*Audit Trial*	*Data Review*
Data Retention	*Archive*	*Backup*	*File Structure*
Flat files	*Related Database*	*Validation - for Intended Purpose*	*Computerized System User Access / System Administrator Roles.*

Diapharm

Strengthening of GMP requirement Excipients: Final EU Guideline published

Guidelines on the formalised risk assessment for ascertaining the appropriate good for excipients of medicinal products for human use" published by European Comission on March 19, 2015. The time frame for implementation of this guideline is listed with one year i.e. by 21 March 2016



Diapharm

Diapharm will build YOUR bridges ...

... and will guide you safely and succesfully
to the **European Health Care market.**

Diapharm

Contact information

Ralf Sibbing
General Manager · Partner

Diapharm GmbH & Co. KG
Hafenweg 18-20 · 48155 Muenster · Germany
Phone: +49(0)251-60935-515 · Mobile: +49(0)160-7123308
ralf.sibbing@diapharm.com · www.diapharm.com

Contact information - China

Diapharm

Prudence Wu
Chief Representative

Diapharm GmbH & Co. KG · Shanghai Representative Office
Unit 1530, L'Avenue Shanghai, 99 XianXia Road, Changning
200051 Shanghai, P.R. China
Phone: +86 (0)21 6057 7019 · Mobile: +86 (0)189 3048 1997
prudence.wu@diapharm.com · www.diapharm.com

Diapharm

Diapharm in China in cooperation with

Diapharm

Join the dialogue!

Diapharm GmbH & Co. KG
Münster / London / Vienna / Shanghai · Hafenweg 18-20 · D-48155 Münster
phone: +49 251 60935-0 · info@diapharm.com · www.diapharm.com

Diapharm

EU market Data derived from the following sources

BPI German Pharmaceutical Industry Association

ims | INTELLIGENCE. APPLIED.

Diapharm