第1回　EMA
国際ナノメディシン
ワークショップ　概要

国立医薬品食品衛生研究所　薬品部
加藤　くみ子　川西　徹

EMA主催　国際ナノメディシンワークショップ

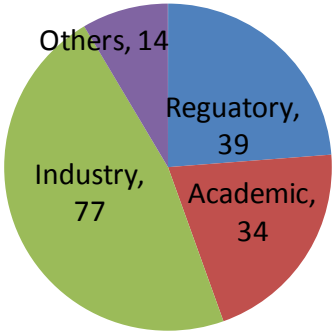
2-3 September 2010: European Medicines Agency 1st International Workshop on Nanomedicines

Scope: The workshop will focus on key features of nanomedicines and the emerging scientific knowledge in the field.

Objective: Explore scientific aspects specific to nanomedicines and share experience at an international level, to anticipate future needs.

Outcome: Report on identified issues and emerging science aspects, which may assist future developments in the field and may be relevant to future regulatory considerations.

Participants:164
Speakers and Chairs: 35



Agenda

1. Special aspects of nanomedicines
   -Development, Manufacturing & Characterisation
2. Special aspects of nanomedicines
   -Non-Clinical Assessment
3. Nanomedicines on the market and in clinical development
4. Emerging nanomedicines
5. Nanomedicines and the application of Risk Management Principles
6. International outlook for Nanomedicines

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2009/12/event_detail_000095.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c3

Session 1: Special aspects of nanomedicines

Development, Manufacturing & Characterisation

・ナノメディシン製造の新しい技術
・ナノメディシンの品質特性評価手法

演者:

・Mamoun Muhammed, Head of Functional Materials Division, and Nano Characterization Centre, Royal Institute of Technology, Stockholm

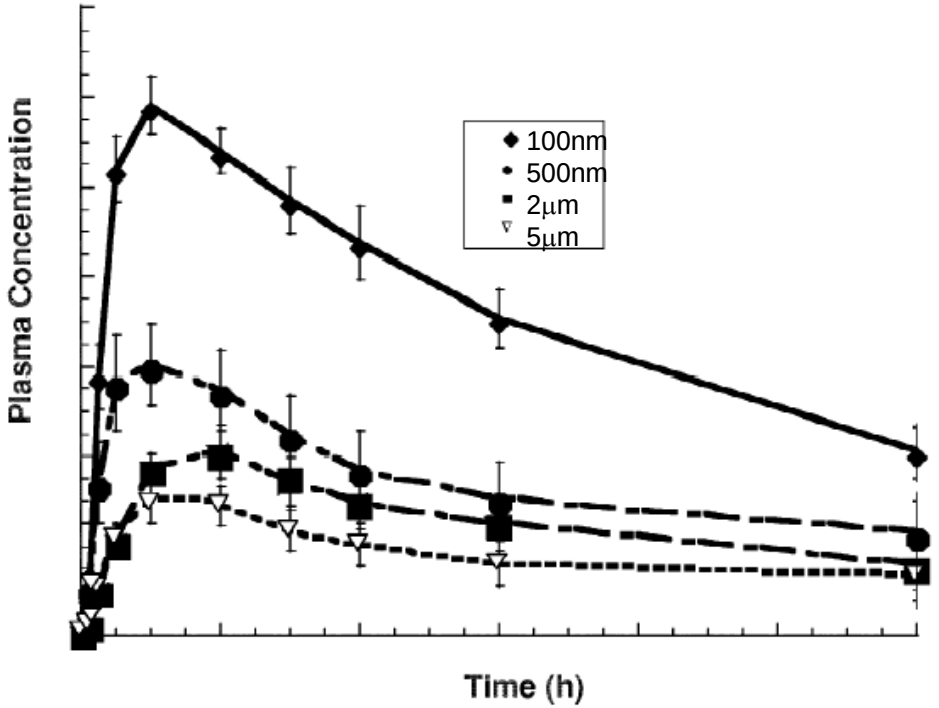
・Simon Holland, GlaxoSmithKline, Director, Process Understanding & Control within GSK Pharmaceutical Development

・Jan Möschwitzer, Abbott Healthcare Products B.V., Head of Early Pharmaceutical Development

Development, Manufacturing & Characterisation

難溶性薬物のナノ結晶化（表面積の増大）

- Increased Bioavailability
- Increased Rate of Absorption
- Reduction in Fed/Fasted Variability
- Dose Proportionality
- Smaller Dosage Form
- Convenient dosage forms



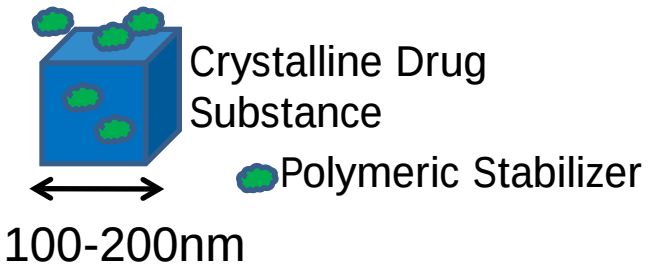
Merisko-Liversidge et al.
European Journal of Pharmaceutical Sciences 18 (2003) 113–120

Development, Manufacturing & Characterisation

難溶性薬物のナノ結晶化 (表面積の増大)

技術:

- Media milling
  - Elan社 Nanocrystal 技術
    - 製品例:Emend (カプセル),
      - Rapamune(タブレット),
      - Megace(経口サスペンジョン)
      - Tricor(タブレット)
      - InvegaSustena(静注製剤)
- High pressure homogenization
- Precipitation
- Super critical fluid
- Cryomilling
- emulsion



Session 1: Special aspects of nanomedicines

Development, Manufacturing & Characterisation　まとめ

1. Nanoparticle characterization techniquesの確立

- Structural analytical techniques
  TEM,SEM, Powder X ray diffraction, Raman spectroscopy
- Thermal techniques
  DSC, TGA, Hot stage microscopy
- Particle size analysis
  Laser reflection, Photon correlation spectroscopy
- Others
  Zeta potential

2. ナノ結晶化医薬品の開発におけるQbDの適用
　現時点では、non-clinical　test(動物でのPK試験）の結果も含めた経験的なアプローチであるが、systematicなアプローチの必要性

Non-Clinical Assessment

・ナノメディシンの生体相互作用
・新たな毒性試験の手法の開発、既存の毒性試験の適用
・In vitroからin vivoへの外挿の妥当性

Speaker:
Wim de Jong, Toxicological pathologist at the Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven

Jacques Descotes, Professor and Head, Poison Center and Pharmacovigilance Department Lyon University Hospitals

Kenneth Dawson, Professor of Physical Chemistry, University College of Dublin, School of Chemistry and Chemical Biology, Dublin

Non-Clinical Assessment

ナノメディシン

難しさ: 様々な、形、サイズ、表面構造

e.g.デンドリマー、フラーレン、量子ドット、ナノ粒子、ナノホーン

⇒ 毒性学的、免疫学的多様性

免疫学的影響

ガイドライン:ICHS8 or ISO TS10993-20(device)

✓Immunusppression (今のところ報告少ない)

マクロファージなどの免疫細胞を抑制

✓Immunostimulation/immunoactivation

サイトカイン遊離など炎症作用の誘起

✓Nonimmune-mediated hypersensitivity

リポソームなど

➢Most current models and assay presumably applicable to some extent even though standardization and adaptation to nanomedicines evaluation obviously needed.

Non-Clinical Assessment

Safety evaluation

細胞構成物と同じサイズ(タンパク質やDNAなど)。
表面積が大きい分、生体との相互作用も増加。

Key issue in risk assessment

- testing and quality control
  Choice of test medium, quality (polydispersity, purity)
- Detection and characterization of nanomaterials is a key
  Chemical composition, Size, Size distribution,
  Agglomeration, Crystallinity...
  Understanding and correlation of size measurement
  techniques.
- ADME
- Interaction with biological systems
  In vivo or in vivo imaging system
  protein adhesion

Session 3: Nanomedicines on the market and in clinical development

Liposomal nanomedicines and innovative formulations
Daan Crommelin, Professor of Pharmaceutics, Utrecht University, and Scientific Director, Dutch Top Institute Pharma, Leiden

Polymer conjugates
Ruth Duncan, Professor Emerita and Past Director Centre for Polymer Therapeutics Cardiff University

Nanoparticles
Rogério Gaspar, Professor of Pharmaceutics, University of Lisbon

Approved-'Liposome'-based Drug Products

Product	Year Approved	API
AmBisome	1990	Amphotericin B
DOXIL/Caelyx	1995	Doxorubicin
ABELCET	1995	Amphotericin B
Daunoxome	1996	Daunorubicin
Visudyne	2000	Verteporfin
Definity	2001	Octafluoropropane
Myocet	2001	Doxorubicin
DepoCyte	2002	Cytarabine
DepoDur	2004	Morphine
Octocog alfa	2009	Factor VIII

Source from presentation by Dr. Daan Crommelin

Evaluation test for quality assurance of liposomal formulation

Assay/Characterization	Methodology/Analytical Target
pH	pH meter
Osmorality	Osmometer
Phospholipid concentration	Lipid phosphorus content/HPLC
Phospholipid concentration	TLC, HPLC
Cholesterol concentration	Cholesterol oxidase assay, HPLC
Drug concentration	HPLC…

Chemical stabiliy	Methodology/Analytical Target
pH	pH meter
Phospholipid peroxidation	Conjugated dienes, lipid peroxides FA composition (GLC)
Phospholipid hydrolysis	HPLC, TLC, FA concentration
Cholesterol autooxidation	HPLC, TLC
Antioxidant degradation	HPLC, TLC

Source from presentation by Dr. Daan Crommelin

Evaluation test for quality assurance of liposomal formulation

Physical stability	Methodology/Analytical Target
Size distribution Submicron range Micron range	 DLS Coulter Counter, light microscopy, Laser diffraction, GEC
Electron surface potential	Zeta-potential measurements
Surface pH	pH sensitive probe
Number of bilayers	SAXS(small angle X-ray scattering), NMR
Percentage of free drug	GEC, IEC, protamine precipitation
Dilution-dependent drug release	Retention loss on dilution
Relevant body fluid induced leakage	GEC, IEC, protamine precipitation
Biological characterization	**Methodology/Analytical Target**
Sterility	Aerobic and anaerobic cultures
Pyrogenicity	Rabbit
Animal toxicity	Monitor survival, histology, pathology

Source from presentation by Dr. Daan Crommelin

Guidance for Industry

Liposome Drug Products

Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register of the notice announcing the availability of the draft guidance.* Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register.*

For questions regarding this draft document contact Liang Zhou, (301) 827-7471.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2002
CMC

Source:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf

Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

Recommended Feb 2010

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Doxorubicin Hydrochloride

Form/Route: Liposome injection/Intravenous

Recommended studies: 2 Studies

Doxil

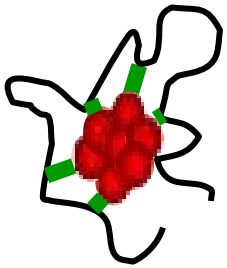
When the test and reference pegylated liposome products

- have the same drug product composition and
- are manufactured by an active liposome loading process with an ammonium sulfate gradient and
- have equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates.

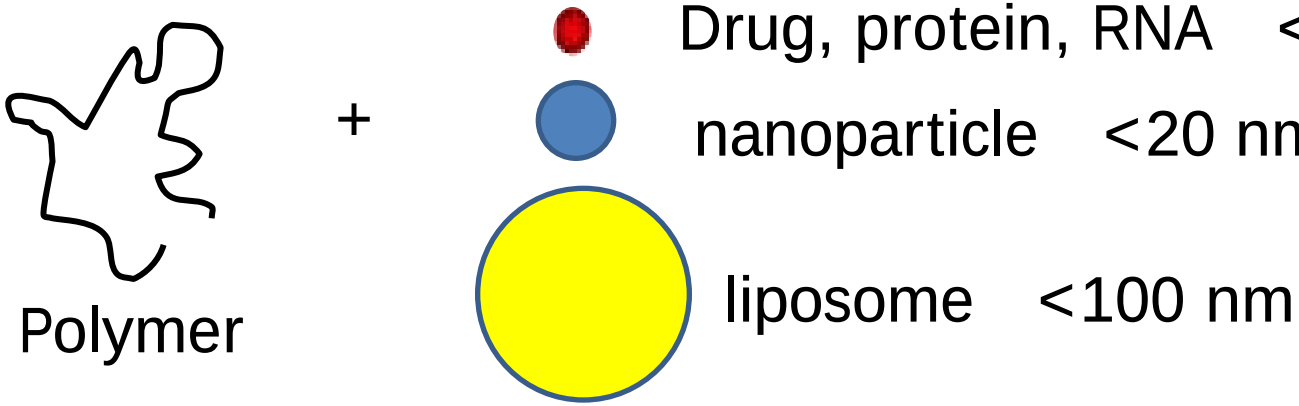
Source:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Polymer conjugates

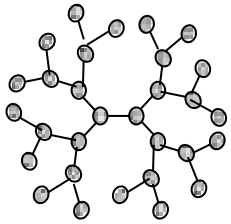
利点：RES（reticuloendothelial system　細網内皮系）の回避⇒ステルス性
薬物放出速度や放出場所等のコントロール(リンカー)。
安定性向上、免疫原性の低減、溶解性の向上

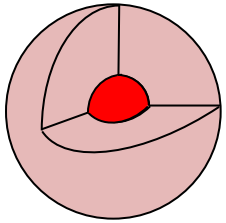


課題：　高分子ポリマーのCharacterization
高分子ポリマーのBiodegradation



Emerging techniques: Dendrimer , Block copolymer





Polymer conjugates

Trade name	compound	Technology	company	indication
SMANCS	Zinostatin Stimalamer	Polymer conjugated protein		
PEGASYS	Peginterferon Alfa-2a（Genetical Recombination）	PEGylated protein	Roche Chugai	Hepatitis C
PegIntron	Peginterferon Alfa-2b（Genetical Recombination）	PEGylated protein	Schering-Plough	Hepatitis C
SOMAVERT	Pegvisomant（Genetical Recombination）	PEGylated protein	Pfizer	Acromegaly
Macugen	Pegaptanib sodium	PEGylated oligo RNA	Pfizer	Age-related macular degeneration

Nanoparticle

- MRI contrast agents
  - ✓Cliavist/Resovist (iron oxide coatedwith carboxydextran)
  - ✓Endorem/Feridex (iron oxide associated with dextran)
  - ✓Combix/Sinerem (ultra small supermagnetic iron oxide: USPIO)
- Nanocrystal
  - ✓Emend (Apretant)
  - ✓Rapamune (rapamycin)
  - ✓Megace (Megestrol)
  - ✓Tricor (Fenofibrate)
  - ✓InvegaSustena(paliperidone palmitate)
  - ✓Triglide(Fenofibrate)
  - ✓Phase II –III: at least 4 products
- Albumin nanoparticle
  - ✓Abraxane

Source from presentation by Dr. Rogerio Sa Gaspar

Session 4: Emerging nanomedicines

新たな技術を用いたナノメディシンと課題

Polymeric Micelles from bench to bedside
Speaker: Alexander Kabanov, Professor, University of Nebraska Medical Center

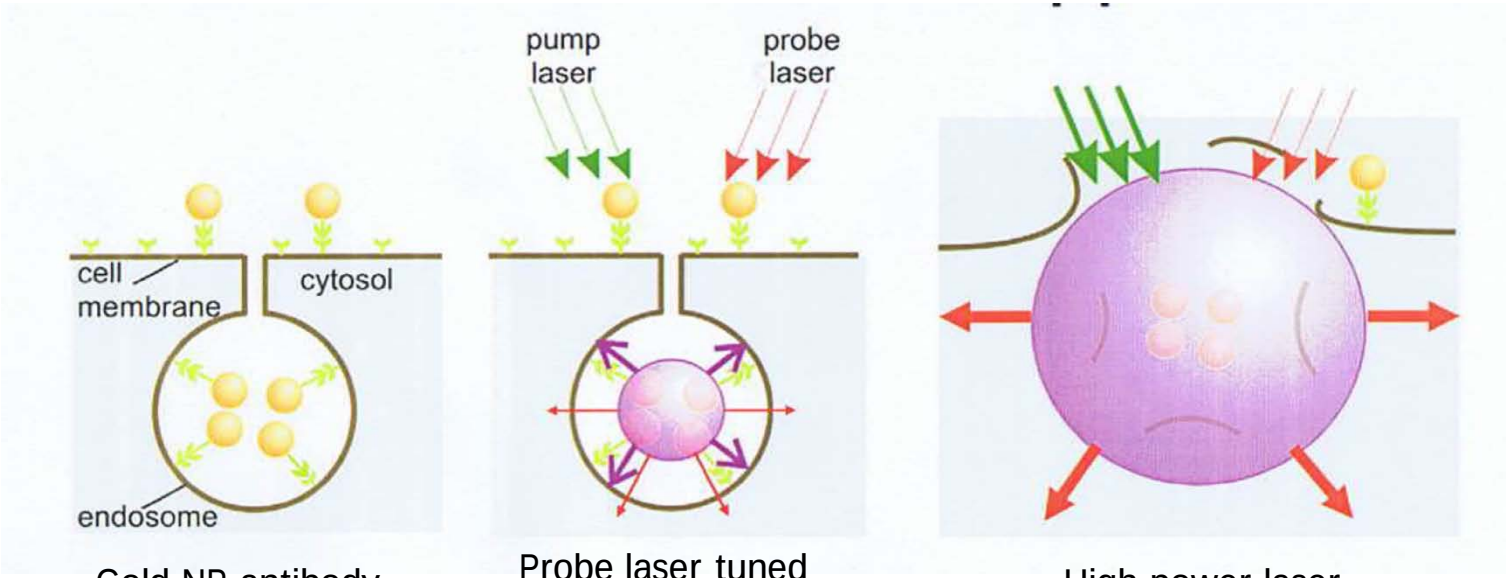
Nanosystems in regenerative medicine
Speaker: Jöns Hilborn, Professor of Polymer Chemistry and Research Coordinator on Polymer Chemistry, Uppsala University

Theranostics nanoparticles (therapeutic and diagnostic)
Speaker: Peter Dobson, Academic Director, Oxford University Begbroke Science Park

Theranostics nanoparticles (therapeutic + diagnostic)

Therapy: Drug release, Hyperthermia, X-ray, Free radial
Imaging: MRI, Fluorescence, Ultrasound

Drug Or Device?
Science fills gaps.



Gold NP-antibody Conjugates taken into cell

Probe laser tuned to plasmon resonance creates diagnostic image via light scattering

High power laser pulse can be used to destroy the cell

Lukianova-Hleb et al. Nanotechnology 21,1-10, 2010

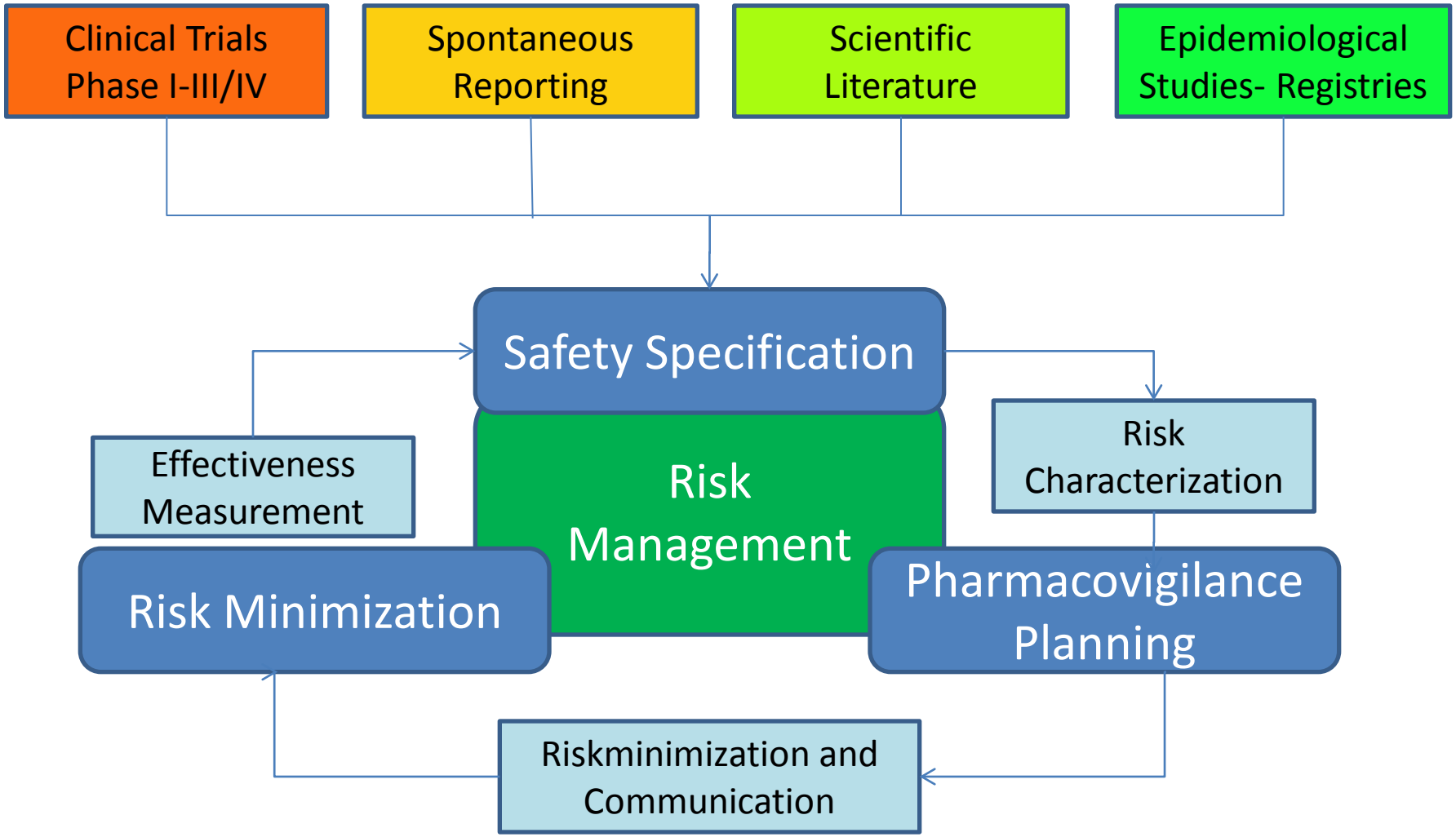
Management of Risks to Patients

Safety Specification - Identification and Methodology
Speaker: Thomas Goedecke, Risk Management Section, European Medicines Agency

Pharmacovigilance and Risk Minimization Plans
Speaker: Jan Petracek, tbc

Environmental Risk Assessment

Specific Methodological Issues and Implications for Risk Assessment
Speaker: Petra Apel, Scientist at the unit Environmental Risk Assessment of Pharmaceuticals, German Federal Environment Agency



Source from presentation by Dr. Amalisa Rubino

EU-RMP Structure

Part I

Safety Specification (ICH E2E)
+ additional EU-specific requirements
Pharmacovigilance Plan (ICHE2E)

Part II

Evaluation of need for additional risk minimization activities
- Risk Minimization Plan (if needed)
- Effectiveness of Risk Minimization Measures

Source from presentation by Dr. Amalisa Rubino

- The current EU-RMP frame work is flexible enough to accommodate nanomedicines specific risks

- Because of their novelty, complexity and technical specificity nanomedicines may imply new, unknown risks to patients.

- New Guidance would support a comprehensive description of nano-specific risks in the Safety Specification

⇒ basis for pharmacovigilance and risk minimization planning

Source from presentation by Dr. Amalisa Rubino

Checklist for nano-specific risks (example)

- Quality characteristics of final product
- Stability
- Administration procedures
- Interactions medicine/patient
  (immunogenicity, tumorgenicity, inflammation etc.)
- Biodegradation, bioaccumulation, organ toxicity
- Biopersistence of nanomaterials (and degradation products)
  (Long –term safety, autoimmunity etc.)
- Re-administration (immune reactions, anaphylaxis etc.)
- Parent-child transmission
- Environmental exposures
- Specific risks which do not fit in existing sections of EU-RMP could be discussed.

Source from presentation by Dr. Amalisa Rubino

Environmental risk management of nanomedicines (EU)

- Nanopharmaceuticals need to undergo an ERA.
- The current ERA approach needs adaptations.
- Input and information is expected from the OECD working party on manufactured nanomaterials*.

*Established in 2006 to develop methods to ensure human health and environmental safety

- Applicant should submit in the ERA part of the application as much information as available on
  - ✓ADME (metabolism excretion)
  - ✓Fate and effects in the environment (e.g. scientific literature)
  - ✓Information from stability tests of other quality tests might also be helpful
    - •Physico-chemical properties,
    - •Biodegradable
    - •Analytical procedures and method

Source from presentation by Dr. Silvia Berkner

Session 6: International outlook for Nanomedicines

An overview of the regulatory approaches and perspectives from different regulatory agencies

Current initiatives in the US

Carlos Peña, FDA

Current initiatives in Japan

Kumiko Sakai-Kato and Toru Kawanishi,
National Institute of Health Sciences/MHLW

Current initiatives in Canada

Duc Vu, Health Canada

Current initiatives in the US

- A number of nanomedicine relevant products are approved and currently on the market (22products)
- The existing regulatory framework can accommodate the types of nanoparticle therapeutics under development and when needed, adapt to address new challenges
- Current published guidances may be applicable to nanoparticle therapeutics
- Staff are working on addressing the need for guidance documents that address nano-related issues as well as the regulatory science to bring to bear to this emerging technology
  - Development of a MaPP on collection of information on nanomedicines in CMC review-completed (CDER)
  - Development of a comprehensive database of approved drugs and drugs under review-in progress (CDER)
- FDA continues to encourage and participate in stakeholder dialogues

Source from presentation by Dr. Carlos Peña

Session 6: International outlook for Nanomedicines

FDA

MaPP on collection of information on nanomedicines in CMC review

Attachment A: Nanotechnology Product Evaluating Questions

1) This review contains new information added to the table below: _____Yes _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____

Current initiatives in Japan

1. The regulation of medicines at the Ministry of Health, Labour and Walfare (MHLW) / the Pharmaceuticals and Medical Devices Agency (PMDA)

2. MHLW activities with respect to nanomedicines

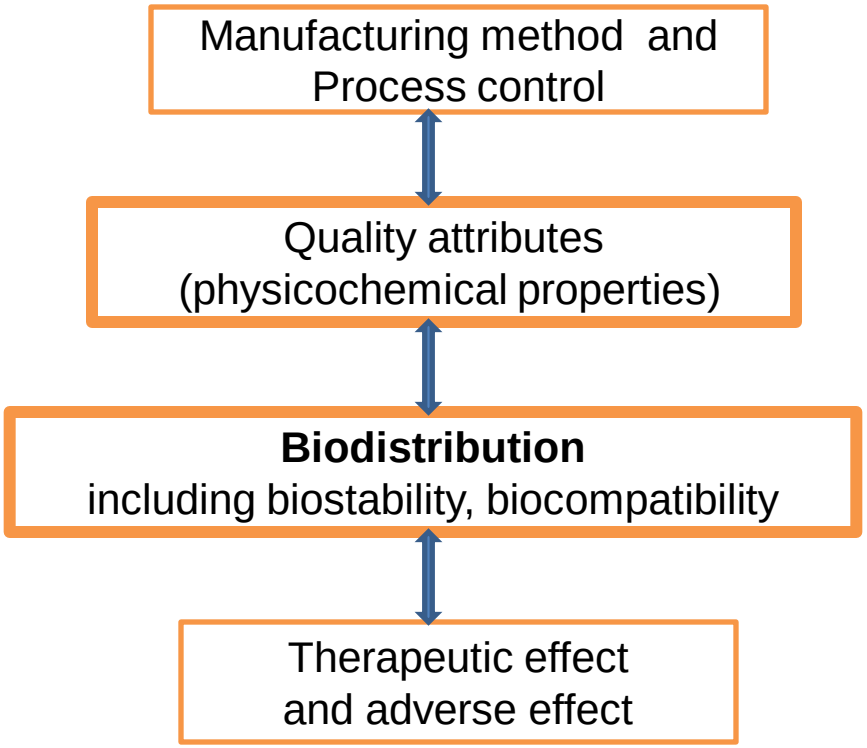
3. Nanomedicines in Japan

4. Future issues for nanomedicines

Study of evaluating and ensuring the quality of nanomedicines

Objective: Development of an evaluation strategy of nanomedicines from the standpoint of quality, efficacy and safety

Nanomedicines are mainly developed for control of biodistribution of APIs



Knowledge about the relationship between each element is important for ensuring efficacy and safety as medicines.

Especially, knowledge about biodistribution is considered to be the key.

Current initiatives in Japan

Future Issue

- ✓ Kick-off discussions will begin among MHLW regulators, PMDA reviewers, and NIHS researchers about the regulation of nanomedicines.
- ✓ Research should be promoted especially in the area of analytical method of nanoparticles and the evaluation method of biodistribution of nanomedicines in the human body. In this research, discussion should take place about the regulation of nanomedicines.
- ✓ Open discussion would be followed between industry, academia, and regulatory authorities about the appropriate regulation of nanomedicines, for enhancing the medical applications of this technology.
- ✓ International cooperation with other organizations.

Current initiatives in Canada

- Interim Policy Statement on Health Canada's Working definition for nanomaterials release for comment (February , 2010)

- Requirement for disclosure of nanomaterials on drug submissions, including clinical trial applications (April, 2010)

- 10 medicines approved that may contain nanomaterials

- Elements of improving Post-marketing surveilance
  - ✓Strengthen labelling requirements
  - ✓Improved adverse reaction reporting
  - ✓Use of strategies to manage and mitigating risk

Source from presentation by Dr. Duc Vu

Session 6: International outlook for Nanomedicines

Health Canada

Drug Submission Application Form for:
Human, Veterinary or Disinfectant Drugs and
Clinical Trial Application/Attestation

59. Is any ingredient listed under Section 56 or 57 a Nanomaterial? ☐ Yes ☐ No

If Yes, provide the name of the ingredient:

60 Dosage Form

provided that the required information or attestations are included in the application.

59	Select the appropriate option based on Health Canada's working definition of Nanomaterials: Health Canada considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if: • It is at or within the nanoscale in at least one spatial dimension, or; • It is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena. For the purposes of this definition: • The term "nanoscale" means 1 to 100 nanometres, inclusive; • The term "nanoscale phenomena" means properties of the product, material, substance, ingredient, device, system or structure which are attributable to its size and distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and, • The term "manufactured" includes engineering processes and control of matter and processes at the nanoscale.

Working Definition

Way forward

What we learned

- これまで“ナノメディシン”の評価は、ベネフィットーリスク　バランスの概念をベースとした現行の規制の枠組みの中で行われてきたが、これが妥当であったことが確認された。

- また、既存のガイドラインを補完する形で新たな評価手法も取り入れられてきている。

- しかし、“ナノメディシン”は非常に多様性に富んでいるがゆえの難しさがある。今後発展し新たに現れるであろうナノメディシンの評価は、既存の知識では対応できない可能性も十分にありうる。そのギャップを埋めるためにも、更なる科学的研究が不可欠である。

Source from presentation by Dr. Marisa Papaluca

Way forward

Challenges

- ナノメディシンは、新たな物理的・化学的要素を入れ込むことにより多機能を付加し、細胞あるいは生体分子との相互作用を巧妙に利用した医薬品である。⇒細胞あるいは生体分子とナノメディシンとの相互作用に関する科学的知見が重要であり、これらは蓄積されつつある。

- ナノメディシンは将来医薬品の概念に影響を与えうるような効果をもたらす可能性を秘めている: これまでに確立されたベネフィット・リスクの手法に基づいた規制要件も適宜、発展しうるべきであろう。

- ナノテクノロジーは急速に、またグローバルに様々な分野で発展している。規制に携わる科学者は、常に適切な評価手法について情報を得、対応する必要がある。

Source from presentation by Dr. Marisa Papaluca

Way forward

Way Forward

1. 規制当局、アカデミア、開発企業間での対話、知識共有の促進

2. 国際的なワークショップを開催することにより:
   a) 新たに現れつつあるナノメディシンに関する情報を得る
   b) 市民社会を引き込む
   c) 患者、市民社会のニーズを知る
   d)非常に複雑な科学を市民社会に伝えるための共通言語を作り上げていく

3. 規制側による専門的知識習得
   a) リスクとベネフィットの明確化
   b) 新たな手法に関する評価
   c) 高度な科学的助言
   d) 申請データを適切に評価
   e) リスク評価とリスク最小限化の手法作成

Source from presentation by Dr. Marisa papaluca

Way Forward

4. 分野横断的に規制の基盤を広げていく
    a) 規制に関わる理解、活動を共有
    b) 関連組織との知識共有
    c) 規制要件に関する意見合致の促進
    d) ボーダーライン製品に関する知識習得

5. ナノメディシンに関わる規制科学についての知識や技術をグローバルに共有し、また議論する

Source from presentation by Dr. Marisa Papaluca