Quality assurance and quality management systems (including documentations)

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TRAINING COURSE OF RADIOPHARMACY
Certified program
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The outline of the lecture

- What is QA?
- What is purpose of the implementation QA concept?
- What are Radiopharmaceuticals?
- What make complexity for defining for radiopharmaceuticals?
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- Why the approach in QA depend on type of radiopharmaceuticals?
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- What differs the radiation therapy & radiopharmaceuticals from non-radiated medicines?
- How we can implement the QA concept in n entire product life-cycle?

- What is the mission of QA concept in Nuclear Medicine Sectors?
- How to make assessment for radiopharmaceutical standards?
- How QA and QC interplay?
- How QA execute its own mission?
- Where is the position of QA Sector in Pharma Company/ Health-care Institution?
- How should be the approach to QA concept in the changing regulatory environment?
- Where to implement regulatory guidelines for building the QA concept?
- Which differences determine the regulations for approaching to QA concept?
- What are improvements in regulatory environment for Implementation the QA concept?
- What is the focus of the QA framework?
- To whom have to be addressed the QA process?

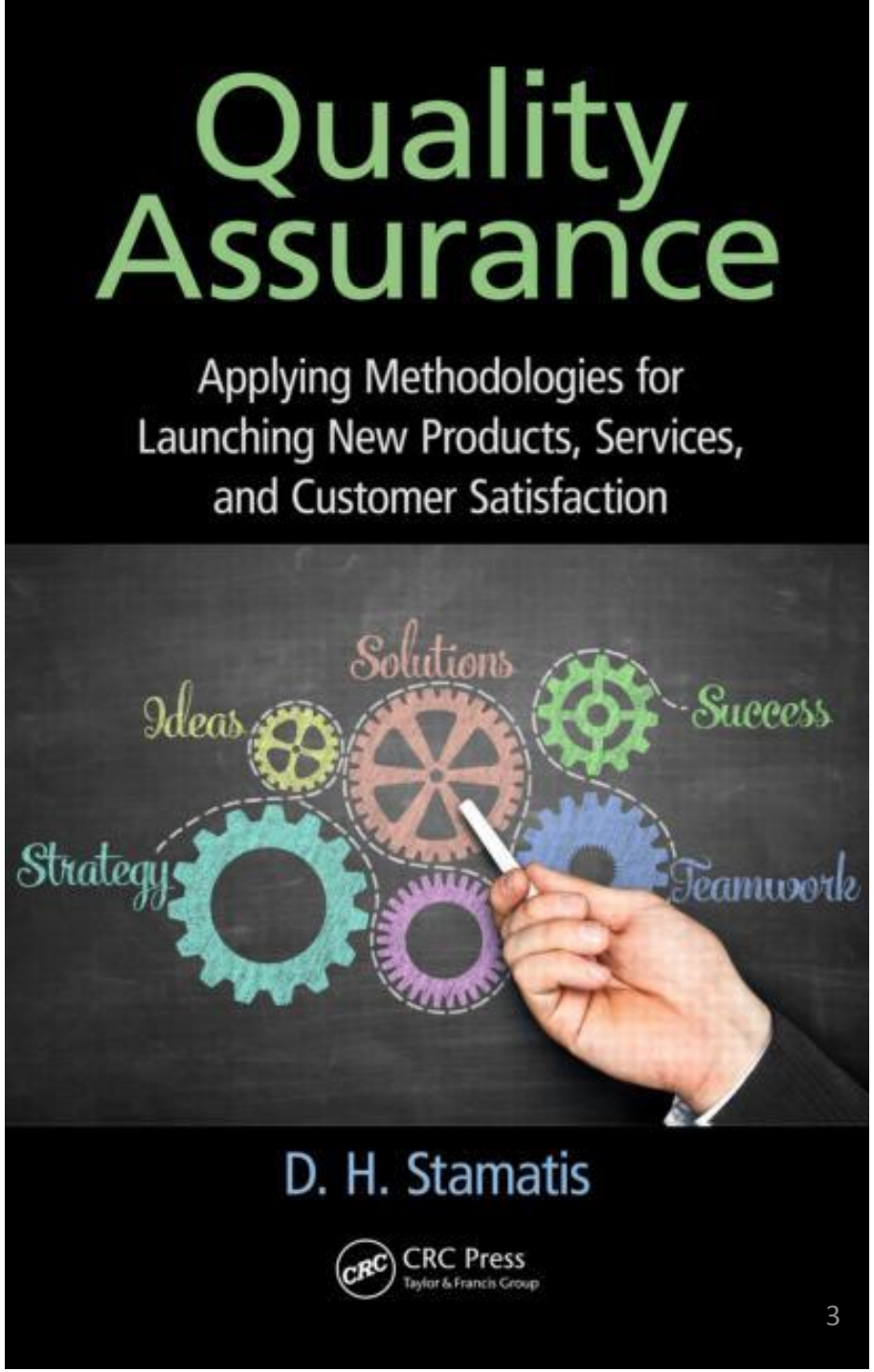
What is QA?

What are these methodologies for being applied in launching:

- **new products,**
- **services and**
- **patient/therapy outcome?**

- **Strategy,**
- **Ideas,**
- **Solutions,**
- **Framework,**
- **Success**

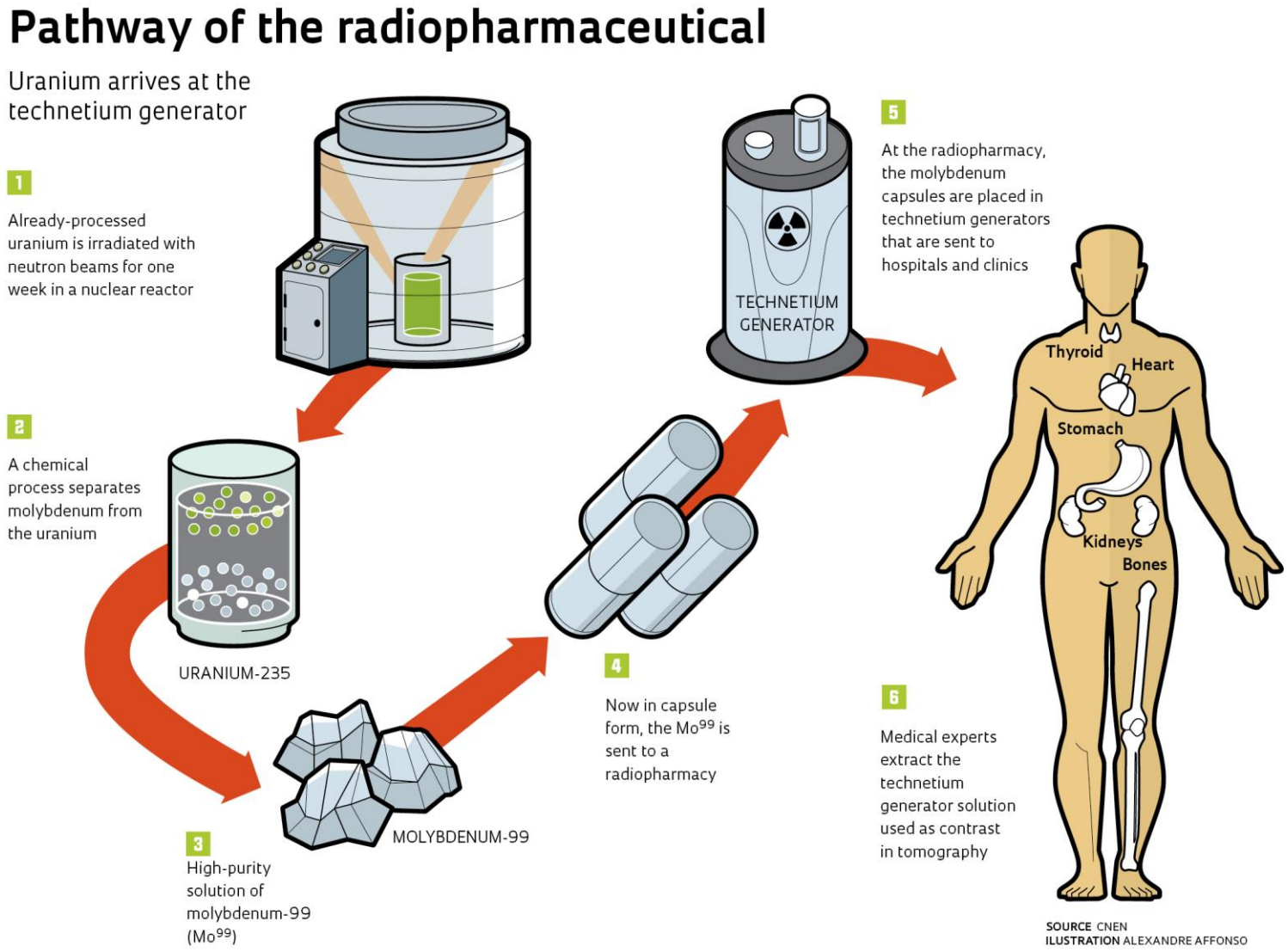
For <u>assuring</u> and <u>proving</u> the Quality



What is purpose of the implementation QA concept?

High efficiency **for high quality drugs to the market in a timely manner**

Safety in entire product life-cycle



What are Radiopharmaceuticals?

Medicinal product which contains or which generates a radioactive substance and which is, contains or generates that substance in order, when administered to a human being, to utilize the radiation emitted therefrom.

Source:

Quality Assurance of Aseptic Preparation Services. Current edition. Ed. A.M.Beaney on behalf of NHS Pharmaceutical Quality Assurance Committee. http://www.rpharms.com/unsecure-support-resources/quality-assurance-of-aseptic-preparation-services.asp? (accessed 7.11.16)

The Medicines (Administration of Radioactive Substances) (MARS) Regulations 1978

What make complexity for defining for radiopharmaceuticals?

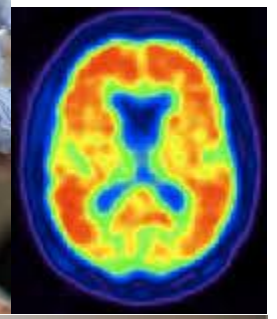
Radio-Pharmacy Unit

Nuclear Medicine Unit

Radiopharmaceuticals dosage forms

Radiotracers = Radiopharmaceuticals

Purpose (Diagnosis & Therapy):
Utilization of radioactive emission for non-invasive imaging and mapping organ & metabolic functions and disease states and dysfunctions, malfunction



The range of radioisotopes, safe for humans and the accessibility for their production determines the extent for application of diagnosis and therapy in Nuclear Medicine

What make complexity for defining for radiopharmaceuticals?

Radioisotope reactors

Medium-; high- flux research & industrial reactors

Molybdenum-99
(4 technetium-99)
Iodine-131
Phosphorous-32
Chromium-51
Strontium-89
Samarium-152
Rhenium-186
Lutetium-177

Cyclotrons – long-lived radioisotopes for imaging diagnostics
medium to high energy (20-70 MeV) with high beam currents were needed.
Single photon emission computed tomography (SPECT).
Thallium-201, iodine-123 and indium-111, radiolabelled glucose
Low energy cyclotrons (9-19 MeV) exclusively for the production of short lived PET:
fluorine-18, carbon-11, nitrogen-13 and oxygen-15

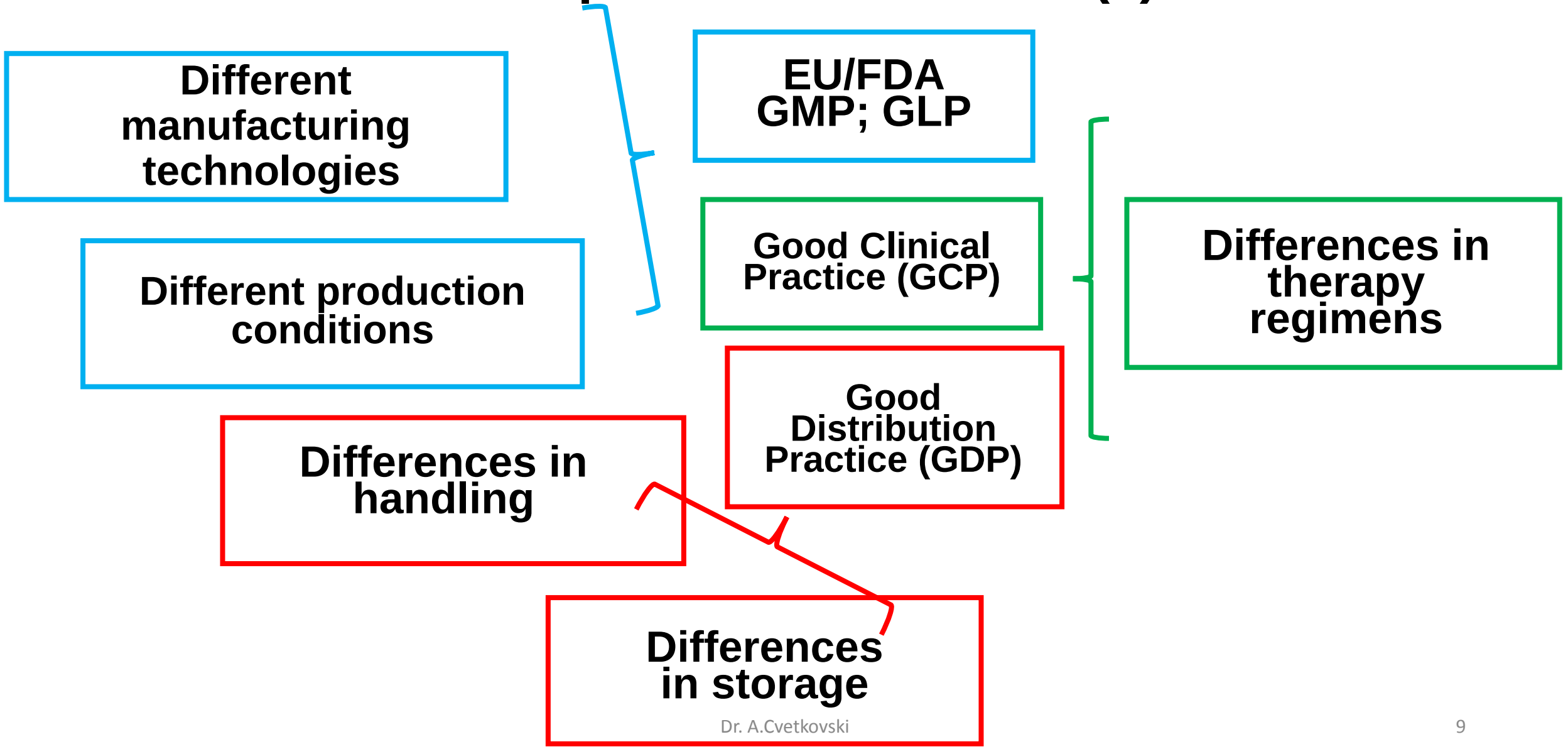
Why the approach in QA depend on type of radiopharmaceuticals? (1)

Radiopharmaceuticals can be classified into four categories:

1. **Ready-for-use radioactive products**
2. **Radionuclide generators**
3. **Non-radioactive components ("kits") for the preparation of labelled compounds with a radioactive component (usually the eluted from a radionuclide generator)**
4. **Precursors used for radiolabelling other substances before administration (e.g. samples from patients)**

Inorganic compounds, organic compounds, peptides, proteins, monoclonal antibodies and fragments, and oligonucleotides labelled with radionuclides with halflives from a few seconds to several days

Why the approach in QA depend on type of radiopharmaceuticals? (2)

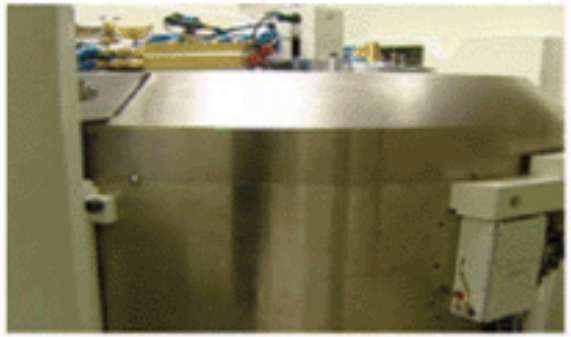


13 MeV cyclotron (indigenous product) in operation in Chosun University, Republic of Korea

Medical isotope production

PARTICLE ACCELERATORS (CYCLOTRONS)

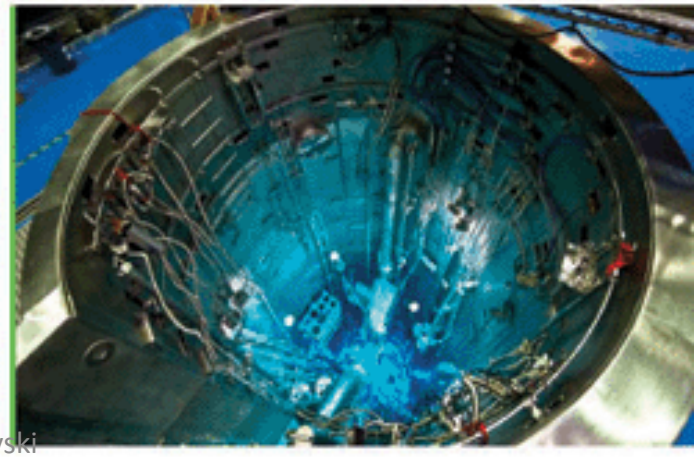
- Specifically made to produce medical isotopes. Relatively cheap
- Produce negligible amounts of wastes
- Production is decentralised – conveniently located at hospitals
- No transport risks
- Not dangerous
- No weapons proliferation risks



The few other isotopes can be made by accelerator-driven systems

NUCLEAR REACTOR (LUCAS HEIGHTS)

- Expensive. Medical isotopes only a side product.
- Produces radioactive wastes
- Centrally located
- Transport problems, especially for short-lived isotopes.
- Wastes a weapons proliferation risk
- Terrorism target



What differs the radiation therapy & radiopharmaceuticals from non-radiated medicines?

Radioactive emission

– Limited handling

– Easily assay of the dose (quantification of API)

– Limitations to some tests – e.g. **sterility**

Immediately available dosage forms (radioactive dose decay!)

– Can’t wait for all test data to be available

– Heavy reliance on Quality Assurance

– BUT no time for large bio burden to accumulate

What differs the radiation therapy & radiopharmaceuticals from non-radiated medicines?

Release has to be done before all data available (e.g. sterility testing)

- **Personnel involved not always pharmacy staff**
- **Small numbers of staff meant Production and release has overlapped**
- **Confusion exists about who can release**
- **‘Retrospective release’ was born!**

Chemical quantities trace BUT making a new chemical entity

- **Pharmacological effects rare**
- **Mainly used for diagnostic purposes**
- **Often see impurities on scan**
- **Implications of impurities not well defined**
- **All the above leads to…….Having the idea Radiochemical Purity isn’t important**

– Patient isn’t a suitable vehicle for product testing!

How we can implement the QA concept in entire product life-cycle?

Toward the Quality Management System (QMS):

- **to implement effective, efficient, transparent and simple processes and structures to achieve continual compliance.**
- **to improve quality, optimized costs, inspection readiness and therapy outcomes.**

By

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M. Pharm, Ph.D. (U.S.A.), Dip. Trg. & Dev. (I.S.T.D)

NIRALI PRAKASHAN

What is the mission of QA concept in Nuclear Medicine Sectors?

- To establish radiopharmaceutical standards

How to make assessment for radiopharmaceutical standards?

Tracking a QC program (specification for testing quality)

- Radionuclidic identity
- Radiochemical identity
- Visual Inspection
- Radiochemical purity
- Radioassay
- Chemical purity
  - Residual solvents
  - Phase transfer catalyst
  - Chloro-deoxyglucose
  - Fludeoxyglucose [^{18}F]*FDG*
- Pyrogen
- Sterility
- Filter integrity
- Product stability

QA guarantee to meet the final product/ service quality by tracking the QC specification

Owen F, Maidment D (1996) Quality Assurance: A Guide to the Application of ISO 9001 to Process Plant Projects (2nd Edition ed.) Rugby, Institution of Chemical Engineers, Warwickshire.

Khurshid SJ, Sadiq MZ (1996) Quality Assurance in Nuclear Medicine -Biological Quality Control of Radiopharmaceuticals. Pakistan Journal of Pharmaceutical Sciences 9: 43-54.

Tools: Planned programs, general procedures, SOPs (standard Operational Procedures for execution the QC specifications)

European Commission (2008) EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1 Manufacture of Sterile Medicinal Products (corrected version). EudraLex The Rules Governing Medicinal Products in the European Union.

EANM (2007) Guidelines on Current Good Radiopharmacy Practice (cGrPP) in The Preparation of Radiopharmaceuticals, Version 2, European Association of Nuclear Medicine.

Quality Control (QC) is an essential part of QA

necessary to ensure an adequate QA program to protect patients from unnecessary ionizing radiation

QC is the part of a QA program

Assessment whether the performance level required of the service has been reached by documenting measurements obtained from tests and checks performed in various areas in nuclear medicine, such as all equipment and radiopharmaceuticals. The results obtained from QC may then be compared to pre set standards to make certain that the results are within the established limits. QC may therefore certify that a product is of good quality and fit for its intended use.

EANM (2008) The Radiopharmacy: A Technologist's Guide. Vienna: European Association of Nuclear Medicine. 12. Early PJ, Sodee DB (1995) Principles and

How QA and QC interplay?

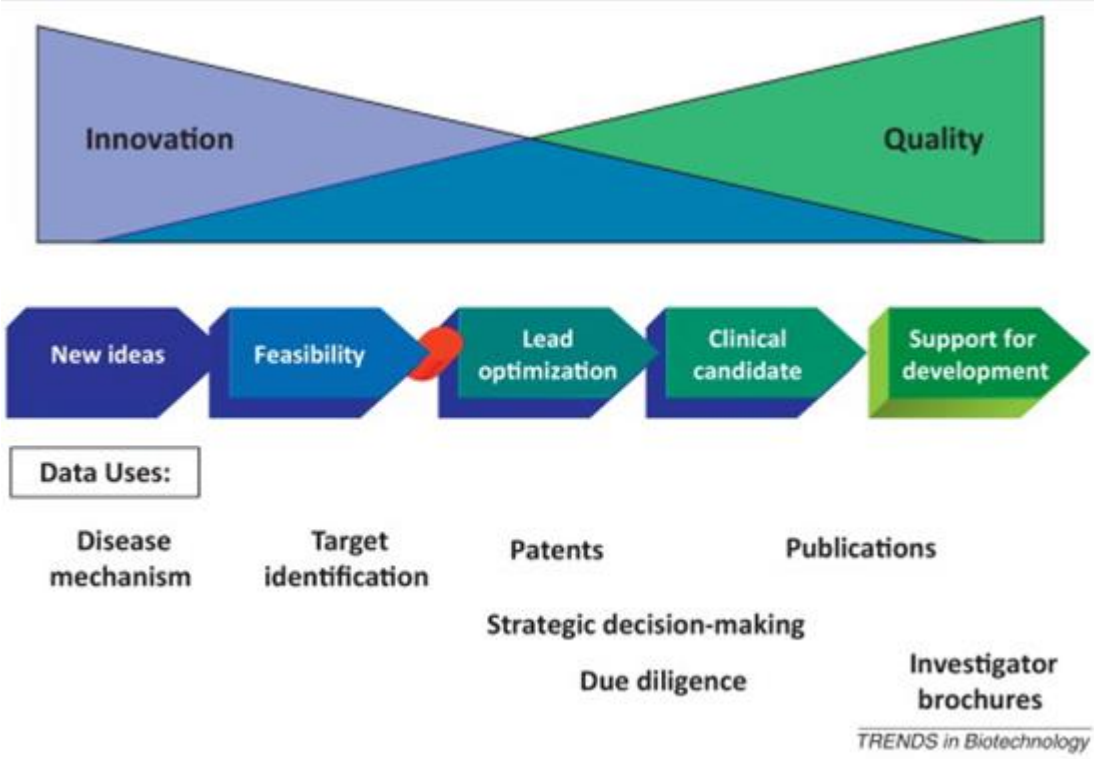
QC	QA
Detect deviation	Prevent deviations
Can change product quality specification	Cannot change product quality specification
On-line activity	Off-line activity
Concerns the operational means to fulfill the quality requirements	Concerns relating to building confidence among stake-holders that requirements for quality will be in compliance to RA and competitive market position

QA in TQM (Total Quality Management)
(QbD – Quality by Design Concept)

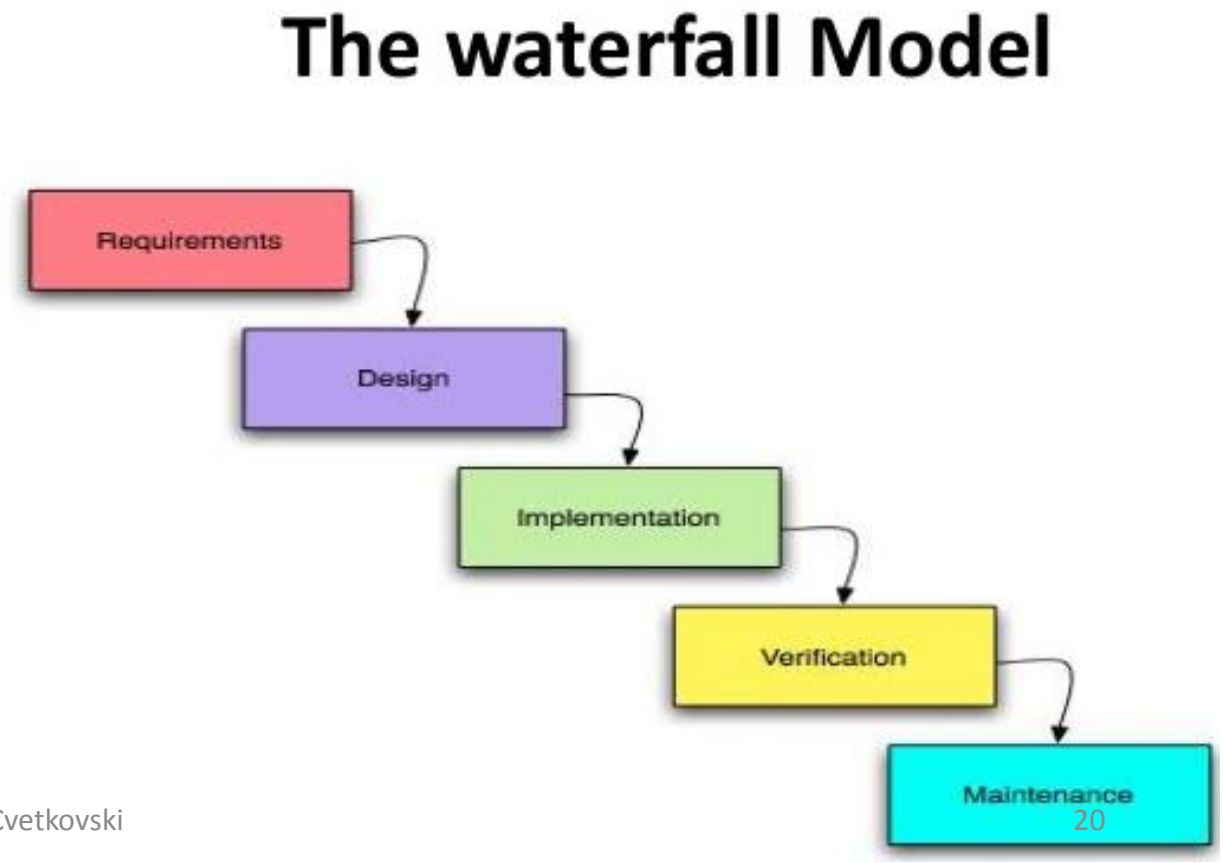
Integrative Approach in Quality Management conducted by QA Methodologies & Tools

Consecutive flow of Interdependent Processes (input / outcome interplay)! 1

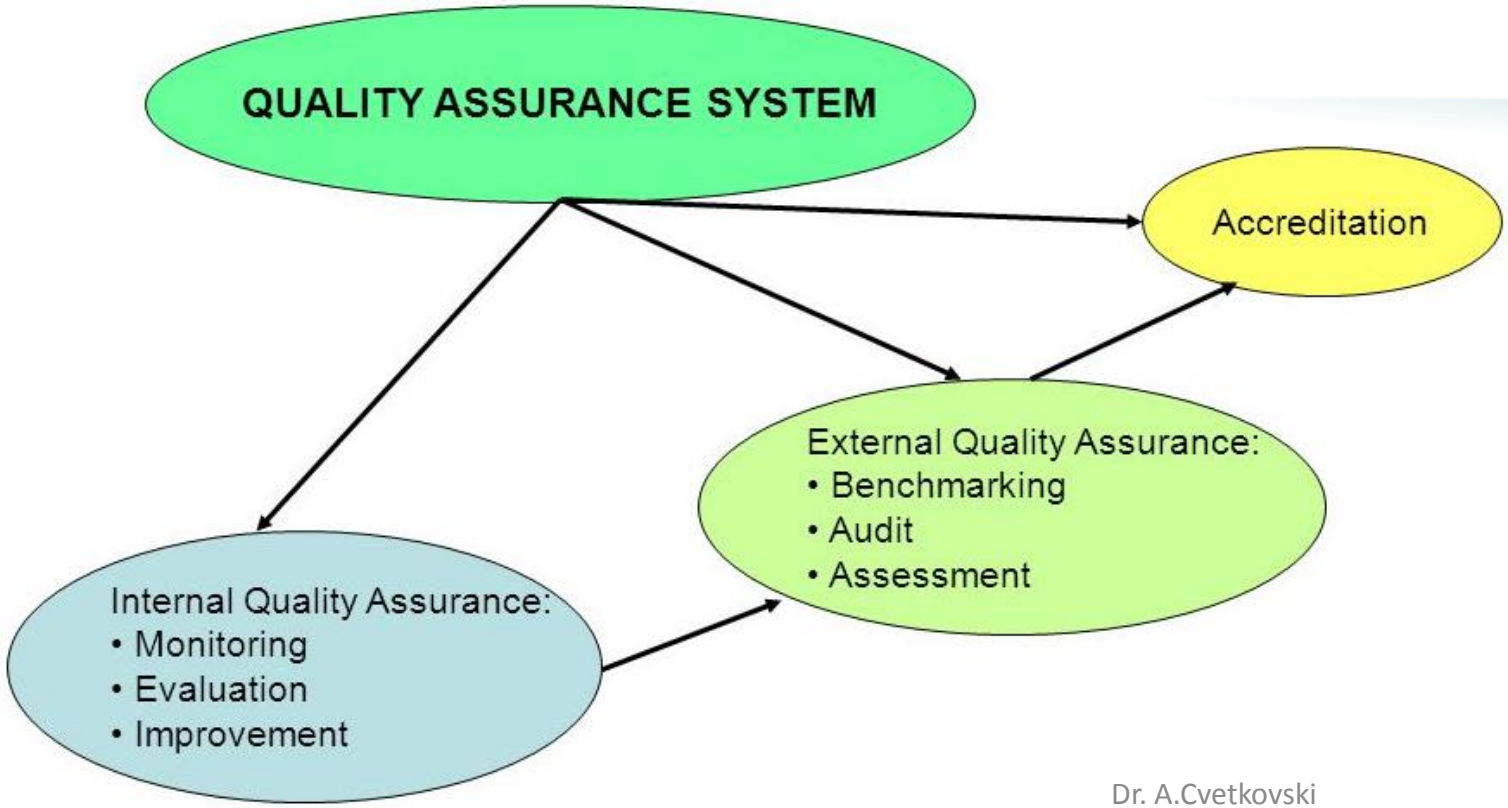
In research-oriented pharma companies/ health-care institutions



General Approach



Consecutive flow of Interdependent Processes (input / outcome interplay)! 2

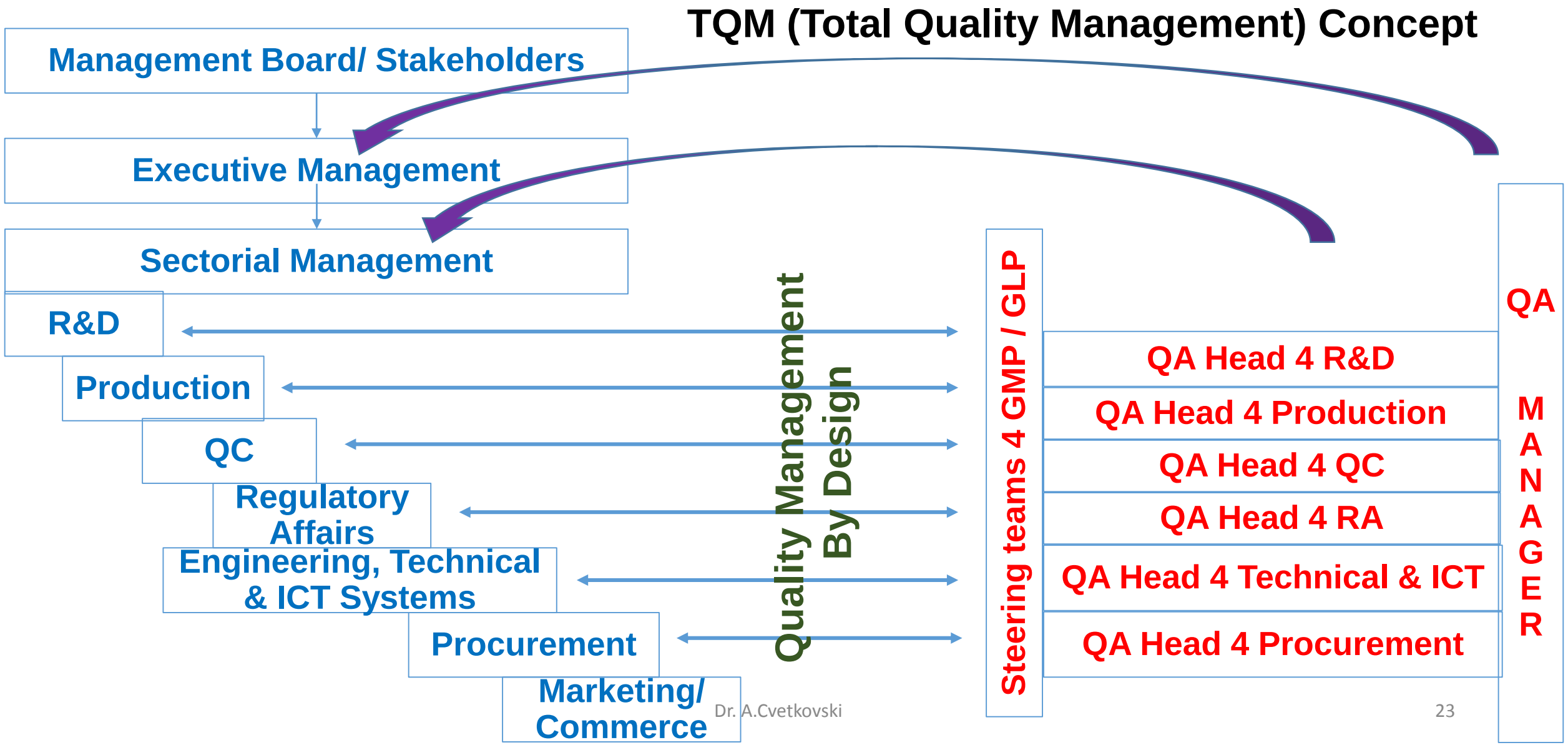


How QA execute its own mission?

Auditing

Survilliance

Where is the position of QA Sector in Pharma Company/ Health-care Institution?



How should be the approach to QA concept in the changing regulatory environment?

- **Pharmaceuticals are complex, multivariate physicochemical systems:**

  - univariant systems (one-factor-at-a-time, trial & error experimental approach) at in R&D stage

- **Physical properties of materials are not always and thoroughly well characterized;**
- **Equipment selection based on tradition;**
- **Process factors are not well understood**
- **Product development usually is done under time & finance constrains;**
- **Post approval changes require regulatory oversight**

Where to implement regulatory guidelines for building the QA concept?

- ***The preparation of radiopharmaceuticals in hospital radiopharmacies;**
- ****The preparation of radiopharmaceuticals in centralized radiopharmacies;**
- **The production of radiopharmaceuticals in nuclear centers and institutes or by industrial manufacturers,**
- *****: The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centers**

*, **: In compliance with the principles of Good Manufacturing Practice (GMP), as specified in European Directive 2003/94/EC and incorporated in the UK into the Medicines Act 1968 (UK). In Radiopharmacies operating under a 'Section 10 exemption' from the Medicines Act where operation under the supervision of a pharmacist is required, compliance with the principles of GMP is audited according to EL (97)52 [4] by an approved Pharmacy Quality Assurance (QA) Specialist. Radiopharmacies with a Manufacturer's 'Specials' License (MS)

***: PET Drugs — Current Good Manufacturing Practice (CGMP)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf

Which differences determine the regulations for approaching to QA concept?

- **The single (1) batch size**
- **Products are often used within 12 hours of preparation**

  (*This makes it impossible to complete all Pharmacopoeia tests prior to release*)
- **Sterility cannot be assured by sterility testing alone.**

  (*Test methodologies for QA of Sterility*)
- **Manufacture may involve the production of a new chemical entity from licensed starting materials.**

  (*Implications for radiochemical purity testing, for releasing the finished products*)

References:

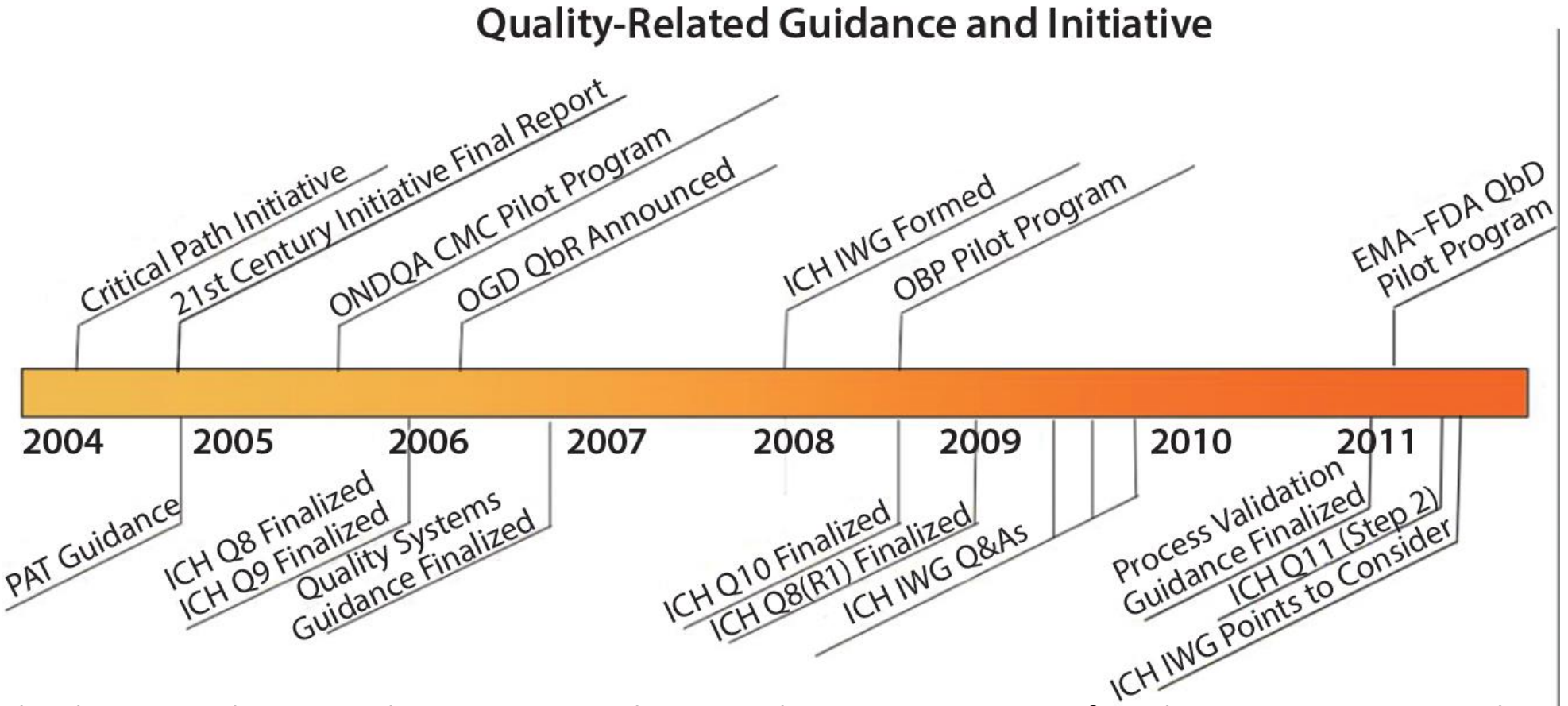
- Rules and Guidance for Pharmaceutical Manufacturers and Distributors. The Stationery Office. London 2007
- Eudralex http://ec.europa.eu/health/documents/eudralex/index_en.htm accessed July 2011
- Quality Assurance of Aseptic Preparation Services 4th edition. Editor Beaney A. The Pharmaceutical Press. 2006.
- Aseptic Dispensing for NHS Patients. PL/CPhO(94)2. Department of Health. 1994.
- Pharmaceutical Isolators Edited by Midcalf B, Phillips WM, Neiger J and Coles T. The Pharmaceutical Press 2004.

What are improvements in regulatory environment for Implementation the QA concept? (1)

- Science based approach
- Risk management
- QSIT (Quality System Inspection Technique)
- PAT (Process Analytical Technology)

Under the umbrella of the FDA GMP for the 21st century initiative

What are improvements in regulatory environment for Implementation the QA concept? (2)



Quality by design guidances and initiatives timeline; regulatory assessment of applications containing QbD elements — FDA perspective

Miksinski SP. *Regulatory Assessment of Applications Containing QbD Elements: FDA Perspective.*

What are improvements in regulatory environment for Implementation the QA concept? (3)

QSIT and PAT moves the FDA

from reviewing all documentation to a system based inspection

covering the following 6 subsystems:

1. **Quality system**
2. **Facilities and equipment system**
3. **Production system**
4. **Packaging and labeling system**
5. **Laboratory controls system**
6. **Materials system**

True spirit of GMP

Shifting from "testing to document quality" paradigm to a "Continuous Quality Assurance" paradigm

….to ensure "built-in" or "by-design" Quality

Outcome:

improved product quality, reduced manufacturing cycle times, reduced laboratory testing and costs

What are improvements in regulatory environment for Implementation the QA concept? (4)

EN ISO 9001 Quality Management System (QMS) "Quality Systems: Model for quality assurance in design, development, production, installation and servicing" combining ISO and GMP requirements

QMS, part of, e.g. in ICH Q7aguidelines, Section 2.11

"Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel".

ISO 9002:

"It is emphasized that the quality system requirements specified in this International Standard are complementary – not alternative - to the technical (product) specified requirements".

What are improvements in regulatory environment for Implementation the QA concept? (5)

EN ISO 9001 Quality Management System (QMS)

- **Generic;**
- **Business-focused standard: Beneficial for business by ensuring the QMS;**
- **Supports the effective management of quality to an internationally recognized level of best practice;**
- **It is flexible in that it specifies what is to be achieved, but allows each company freedom to determine, and justify, how these requirements are achieved**

Good Manufacturing Practice GMP

- **Industry-specific or manufacturing standard;**
- **Prescribing what should be done to ensure product safety and efficacy;**
- **Ensures that quality is built during the whole manufacturing and control process and that regulatory requirements are met.**

What are improvements in regulatory environment for Implementation the QA concept? (6)

Complementary requirements between QMS and GMP

PIC (Pharmaceutical Inspection Convention, now called PIC/S) GMP Guideline which refers to "... a correctly implemented system of Quality Assurance incorporating GMP ...", and

ISO "..... this international standard is complementary - not alternative - to the technical (product) specified requirements".

PSW 11/2016 Annual Report 2015: https://www.picscheme.org/en/publications

What are improvements in regulatory environment for Implementation the QA concept? (7)

QMS requirements for QA concept

- **Effectiveness** (should have the visible and ongoing support of top management;
- **Beneficial for the business/ company** (should involve all staff whose activities influence quality, have a clear and unambiguous continuous improvement focus, and incorporate relevant, realistic performance measures with emphasis on reducing failure costs, and satisfying (internal and external) customer needs
- **The highest level in the documents hierarchy**: Directory to the QMS, a unique character of the company.

Less paperwork, more effective QMS

Misinterpreted and incorrectly applied standards lead to a bureaucratic and inefficient QMS

What are improvements in regulatory environment for Implementation the QA concept? (8)

ISO 9000:1994

organization's "*capability to design and supply conforming product (where this) needs to be demonstrated*"

ISO 9000:2000

"***ability to consistently provide product that meets customer and applicable regulatory requirements, and aims to enhance customer satisfaction***…."**.**

ISO 9000:1994 & ISO 9000:2000 merged in ISO 9001:2000

- Involvement of "Top Management", (e.g. the Board) in the quality management process;
- Customer satisfaction and continual improvement are of particular concern;
- Promotes the adoption of a process-approach: Processes convert inputs into outputs: Identify, manage, and link to other processes;

The following points should be checked:

- are responsibilities assigned (e.g. process owners nominated)?
- are the procedures implemented and maintained?
- is the process effective and providing the required results?

What are improvements in regulatory environment for Implementation the QA concept? (9)

Relationship between 9001:2000 & ISO 9004:2000

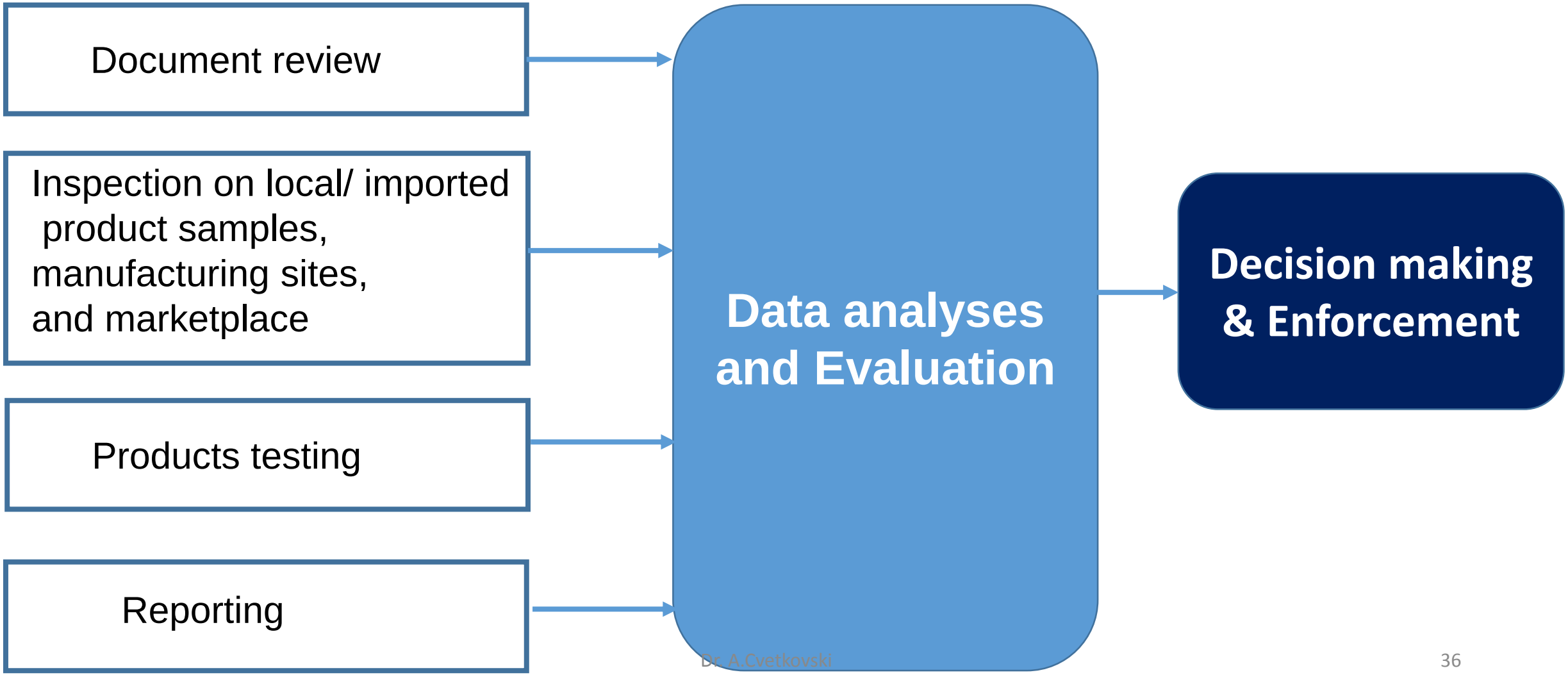
- **ISO 9001:2000 and ISO 9004:2000: two stand-alone documents which were designed to be a consistent pair of standards.**
- **ISO 9001:2000: defines the requirements which have to be fulfilled in order to accomplish compliance with customer needs and continual improvement of the QMS: can be used to achieve third-party certification.**
- **ISO 9004:2000: develops the concept in a more extensive and intensive manner as a roadmap for organizations on their way to excellence with links to:**

the EFQM Business Excellence Model

the Balanced Score Card Approach

Necessary to build QA concept

What is the focus of the QA framework?



To whom have to be addressed the QA process?

To the National Regulatory Authority (e.g. FDA, National Medicinal Agencies)

more enforcement for monitoring of regulation, more effective QA system

Practical Approach for QA

1. **Procedures that ensure the quality of the radiopharmaceuticals on manufacturing site**
2. **Procedures that ensure the purchasing the products that meet recognized standards**
   - **product selection:**
   - **supplier selection**
   - **providing Certificate of Analyses fro each purchased batches**
   - **GMP Certificate (WHO type of certificate**

3. **Procedures to verify that shipped products meets the specifications:**
   - **Pre- / post shipment inspection**
   - **Analytical pharmaceutical testing**

4. **Procedures for monitoring and maintaining the quality of radiopharmaceuticals from the moment they are received until the medicine is finally administered to the patient:**
   - **procedures for proper storage and distribution**
   - **appropriate dispensing**
   - **instruction for proper usage of the product**
   - **product defects and pharmacovigilance reporting program**

Critical Impact Assessment for QA in Radiopharmaceuticals

The preparation of radiopharmaceuticals in a hospital

1. License approval of production site for “Special” manufacturing activities:

   The Medicines Act 1968. HMSO. 1968

2. Supervision of the pharmacist for outsourcing production of the radiopharmaceuticals for clinical trials applications (Investigational medicinal Products/IMP/), in manufacturing unit, approved by the license (Manufacturing Authorization Investigational Medicinal Product License, MA (IMP)

Rules and Guidance for Pharmaceutical Manufacturers and Distributors. The Stationery Office. London 2007
Eudralex http://ec.europa.eu/health/documents/eudralex/index_en.htm accessed July 2011
The Medicines for Human Use (Clinical Trials) Regulations 2004. SI 2004 No. 1031 TSO. London 2004
MHRA.http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/IMP/index.htm

Personnel responsible for implementation of QA

Chief Pharmacist/ Authorized Pharmacist/ Qualified Person

- Monitoring the production site,
- Monitoring the outsourcing/ stipulated activities in contract

Chief of Quality Control

Production Manager

Joint responsibilities of the QC and Production Heads

- Authorization of written procedures and other documents including amendments
- Monitoring and control of the manufacturing environment
- Plant hygiene
- Process validation
- Training
- Approval and monitoring of suppliers and materials
- Approval and monitoring of contract manufacturers
- Design and monitoring of storage conditions for materials and products
- Retention of records
- Monitoring of compliance with the requirements of Good Manufacturing Practice
- Inspection, investigation and taking of samples, in order to monitor factors which may affect the quality of the product

Purchase and testing of starting materials

Chemical and radionuclide precursors, generators, kits and ready-to-use finished products Comparable checking of recorded data (radioactivity, batch number/ lot, quantity, on-site inspection)/ Products or kits with a European Marketing Authorization

The supply of unlicensed relevant medicinal products for individual patients. MHRA Guidance Note No. 14. 2008
16. Guidance for the Purchase and Supply of Unlicensed Medicinal Products 3rd edition. The NHS Pharmaceutical Quality Control Committee. London 2004

When unlicensed products are used, the prescriber must be made aware of their responsibilities, although the purchaser assumes the responsibility for their quality :
Compulsory covered by Marketing Authorization in the European Union (EU) or one with a Mutual Recognition Agreement

Suppliers should be requested to supply a "Certificate of Analysis" (CofA) meeting the requirements of the UK Guidance on Certificates of Analysis

compliance of starting materials with Transmissible Spongiform Encephalopathy (TSE) Regulations and The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [S.I. 2003/1680] & EMA/410/01 rev.3

Implementation of QA on facilities & equipment

Plan & Prevention Maintenance (PPM) on regular base (Installation Qualification-/IQ; Operational-/OQ; Performance-/PQ, part of Validation Master Plan (VMP)

Alarm conditions for monitoring & re-calibrating in the required timeframe

Acceptance criteria (part of OQ and /or PQ) for new calibrators or after major repairs.

Case study 1:

Frequency of radionuclide calibration tests

Parameter	Acceptance	Daily	Annually
High voltage			
Display			
Zero adjust			
Background			
Check source (Relative response)			
Accuracy			
Repeatability			
Subsidiary calibrations			
Linearity			

All spreadsheets and other software solutions used for calculations should be validated, controlled and secure. Comprehensive details of how the various measurements may be made are described in Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and their Quality Control

Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control. Measurement Good Practice Guide No. 93. National Physical Laboratory, Teddington, UK 2006

QA Documentation 1

- A Standard Operating Procedure (SOP) should be written and independently approved for each procedure or activity associated with the operation of the unit.
- Reviewed at specified intervals of typically not longer than two years unless otherwise justified.
- A system of change control should be in place.
- History for operation of the system
- Audit trail should extend from prescription verification to the administration of individual patient doses.
- A staff training manual for all grades of staff should be written and independently approved.
- A specification should be prepared for finished radiopharmaceuticals.
- For IMPs (Investigational Medicinal Products for clinical traials), written specification of starting materials are also required, as part of the Product Specification File.

Record Keeping

a. Purchase of radioactive products and ingredients

b. Generator elution, yield, [99Mo] Molybdenum breakthrough and aluminium ion breakthrough if required

c. Product preparation, QC and release

d. Environmental and microbiological control including aseptic operator validation and trend analysis

e. Aseptic process validation

f. Laboratory cleaning and maintenance

g. Equipment and plant calibration and maintenance

h. Staff training and continuing professional development

i. Transport of radioactive materials [21]

j. Radioactive contamination monitoring and radioactive waste disposal

k. Product defects and SOP non-conformance i.e. when a procedure is performed in a manner other than that described in the relevant SOP

l. Inspections and audits

Environmental Monitoring

Cleanroom facility and associated workstations (Laminar Air Flow Cabinets (LAFCs) and isolators)

‘Physical Testing’ where a parameter of a piece of equipment is measured or as ‘Microbiological Testing’

Aseptic Preparation Services standards

References:

Rules and Guidance for Pharmaceutical Manufacturers Annex 1 ,
ISO 14644 , Pharmaceutical Isolators, Parenteral Society Technical Monograph No 2,
ISO 12469.
Parenteral Society Technical Monograph No. 2. Environmental Contamination Control. The Parenteral Society, Swindon. 1989.
BS EN 12469:2000. Biotechnology - Performance criteria for microbiological safety cabinets. British Standards Institute. London 2000.
Pharmaceutical Isolators Edited by Midcalf B, Phillips WM, Neiger J and Coles T. The Pharmaceutical Press 2004.
Quality Assurance of Aseptic Preparation Services 4th edition. Editor Beaney A. The Pharmaceutical Press. 2006.

Environmental Monitoring Case study 2

Physical Tests

Test	Minumum Frequency
Glove integrity test and/or visual inspection of isolator glove and sleeve assembly	Sessional
Isolator pressure differential and airflow rate	Recorded Daily - measured continously *
Pressure differential across room and workstation HEPA filters	Recorded Daily - measured continuously*
Pressure differential between rooms in aseptic suite and adjacent areas	Recorded Daily - measured continuously *
Isolator pressure decay test (leak test)	Weekly
Isolator alarm test	Weekly
Air velocities of workstation and uniformity of LAFC & laminar flow isolators	3-Monthly
Air change rates of the clean rooms	3-Monthly
Airborne particles in classified rooms	3-Monthly
Workstation & room HEPA filter efficiency & integrity of seals and joints	Yearly
KI discus protection test (LAFCs only)	Yearly

Microbiological Tests

Test	Frequency
Settle plates in critical zones (LAFC/Isolators) in operational state	Sessional
Glove prints / finger dabs in critical zones (LAFC & Isolator) in operational state	Sessional
Settle plates in background environment, room and isolator transfer devices & change facilities in operational state	Weekly
Microbiological surface samples in LAFC/Isolator & Isolator Transfer Device and background environment in operational state	Weekly
Airborne viable organisms in LAFC/isolator, transfer device and background environment	3-Monthly

Finished Product Testing and QA

99mTc kit preparations to British Pharmacopoeia or EP standards is impractical and unnecessary.

Radionuclidic purity
The EP limit is 0.1% (1 kBq 99Mo per MBq 99mTc)
For unlicensed finished products radionuclidic purity should be established according to local protocols

Radiochemical purity (RCP)
RCP testing of products made using non-licensed starting materials is required for every batch / reconstituted kit, unless a validated, GMP-compliant system for manufacture and release is in place.
Routine RCP testing of radiopharmaceuticals made using licensed starting materials is more controversial
New Chemical Entity NCE) should be tested to ensure it is compliant with specifications.

RCP in assessment of:

- Impact of change and investigation of problems: to investigate the impact of problems, such as breakdown of a refrigerator (part of planning validation due to changes)
- Patient Safety: to identify defective products, which can result in patient harm. For example, the use of 99mTc HMPAO for confirmation of brain death. The biodistribution seen where brain death has occurred is identical to that seen with a pertechnetate brain scan.

Radiochemical purity (RCP)

The frequency of RCP testing should be determined locally, taking into account the following risks:

a. Any change, planned or unplanned e.g. new type of kit, change of saline, change in disinfectants, generator manufacturer

b. Off-label manufacture e.g. dilution, adding additional activity

c. Unlicensed Products

d. Cold chain transport of both finished products and cold kits

e. Therapeutic products

f. Kit characteristics e.g. tin content

g. Time since last elution may have an influence for some kit

For radiopharmaceuticals under the Clinical Trials

Products manufactured under an MA (IMP) may require RCP testing in accordance with the Clinical Trial Application (CTA).

- Chemical Purity (aluminum breakthrough)

a Products where the manufacturer specifies a limit for eluate aluminum content e.g. Myoview for which the eluate should contain no more that 5ppm, the European Pharmacopoeia limit.

b Products where drug interactions have been reported e.g. colloidal preparations

- Total radioactivity or radioactive concentration

- Appearance and freedom from gross particulate contamination

- Particle size of particulate radiopharmaceuticals

- Non-filterable activity

- pH

- Defect reporting and Pharmacovigilance

QA for Sterility

To demonstrate that the preparation process in the Radiopharmacy results in an acceptable level of sterility assurance

Sterility assurance may be considered as a collective of a number of testing and monitoring parameters, which might include, but not be restricted to, the following elements: sterility testing, environmental monitoring, validation of the operator's aseptic technique, process validation, end of session broth fills and, where appropriate, pyrogen / endotoxin testing.

Protocols for sterility testing a

Documented action plan should be put into effect to investigate the cause and implement Corrective and Preventative Action (CAPA)

Pyrogen / Endotoxin Testing

Radiopharmaceuticals made from licensed kits are not required to be pyrogen tested.
PET radiopharmaceuticals and some radiolabelled antibodies and peptides that are made from non-sterile starting materials, should be subject to a pyrogen test (as per requirements of the European Pharmacopeia – see individual monographs)

Validation

Validation is the demonstration that a procedure reproducibly achieves its desired outcome. For a new build or refurbishment a Validation Master Plan (VMP) is a GMP requirement. Advice can be found in the national Pharmaceutical QA Committee advisory document, Validation Master Plans

Validation should be undertaken in the following areas:

a. Microbiological validation of processes, facilities and the aseptic technique of operators

b. Transfer of materials into and out of the controlled work zone

c. Cleaning processes

d. Training

e. Computer systems and software

f. Analytical techniques, such as RCP testing

g. Equipment such as TLC scanners, HPLC systems and calibrators

h. Process equipment LAFCs, isolators etc

i. Changing procedures

Operator Validation

Operator validation is performed to demonstrate an individual has satisfactory aseptic technique. Each operator who prepares radiopharmaceuticals should perform the validation test at least every six months.

Process Validation

Process validation must mimic the entire process with substitution of nutrient media in place of starting materials. It is performed to demonstrate that the procedures used to prepare a radiopharmaceutical result in a sterile product. The methodology should be of sufficient complexity to challenge the processes employed during radiopharmaceutical preparation. There may be a need to perform more than one type of test to validate processes that employ different techniques.

Example:

Validation of the process used to prepare a standard 99mTc radiopharmaceutical requires a different test from the process used to prepare 99mTc leucocytes

Training

- A written training program and completion of the training should be documented.
- A system for the evaluation of training should be implemented, focusing in particular on practical skills.
- The employer is also charged with ensuring that staff undertake continuing education and training after qualification.
- The person managing or supervising the unit should review the competencies of staff to perform adequately formally once a year.
- Additional training should be put in place to rectify deficiencies.
- A GMP update should be carried out for all staff at least every 2 years.

Radiopharmacy Training

Initial training should be provided for all staff working in Radiopharmacy departments in the aspects of Quality Assurance and Radiation Safety with which they are involved. This includes staff undertaking:

a. Preparation

b. Release

c. Quality Control and analytical techniques

d. Cleaning

e. Transport

f. Appropriate level of understanding of relevant legislation

The training should be appropriate to the tasks performed and a description of the training and records of completion should be maintained.

Quality Assurance Training

Elements of training should include:

a. An appropriate knowledge of GMP

b. Calibration and monitoring of equipment

c. Working practices in the Radiopharmacy including general Health and Safety and manual handling

d. Competence in the necessary aseptic skills

e. A knowledge of pharmaceutical microbiology

f. Preparation of individual doses

g. Documentation

h. Decay correction calculations

Radiation Safety Training

Regulation 4.4 of the Ionizing Radiation (Medical Exposure) Regulations 2000 mandates the employer to ensure that all operators involved in radiopharmaceutical preparation are appropriately trained, certificated and records kept.

Elements of radiation safety training should include:

a. Working practices in the Radiopharmacy, including radiation Health and Safety and Local Rules

b. Radiation monitoring and protection

c. Dealing with spillages

d. Preparation of individual doses

e. Documentation

Reference:
The Ionizing Radiation (Medical Exposure) Regulations 2000. SI 2000 No. 1059. The Stationary Office 2000, London, as amended.

Release of Radiopharmaceutical Products (1)

A formal, recorded decision of approval must be taken by an authorized person before a product is released for use. In the case of an unlicensed unit this must be an Authorized or Accountable Pharmacist.
In a unit holding a Manufacturer's 'Specials' License (MS), this is the Quality Controller or a suitably trained deputy. The act can be delegated but not the responsibility. In this case, release for use does not have to be carried out by someone with the equivalent level of knowledge to **a Qualified Person (QP),** since they are carrying out a function delegated to them by the Quality Controller. Release and certification of products manufactured under a full Manufacturing License e.g. an IMP license or a Product license cannot be delegated to anyone other than a QP named on the license

The authorized person is not normally the person who prepared the product, although there may be no alternative under emergency situations. Routine expectation is that the person performing delegated release for use function is operationally independent from the production of the product they are releasing on the day of manufacture.

There should be a document detailing the individuals who can perform release for administration / shipment and the provisions in place to ensure independence from manufacturing. The retrospective review conducted by QA/QC should include a review of the continued effectiveness of the release process together with results from sterility, media fills, environmental monitoring, investigations and other indicators of continued compliance such as maintenance and physical monitoring.

Release of Radiopharmaceutical Products (2)

Written procedure for products release. This should state that the person releasing products for use should have an awareness of the current validation status of the unit and any deviations or errors during the process.

Release can only be effected if the product:

a. Complies with the release specification.

b. Has been prepared according to Good Manufacturing Practice (GMP).

There should be a written procedure for dealing with products failing to meet the required standard. Such events are documented and investigated.
There should be a written procedure for the recall of defective products.

The recall procedure should be tested annually.

Inspection and Audit

Requirement for a system of recorded self-inspection

It is necessary that self-inspections should be conducted in an independent way.

Whilst the manager of a radiopharmacy unit and the associated quality controller may operate a local system of self-inspection, a regular (every 12-18 months) audit of a unit not covered by a manufacturer's licence must be carried out by Regional Quality Assurance Specialists (*Executive Letter EL (97)52. Aseptic Dispensing in NHS Hospitals. Department of Health. 1997)*

A unit with a manufacturer's licence undergoes regular inspection by the MHRA on a risk-based frequency but should also undergo an annual audit by an independent person possessing the appropriate pharmaceutical expertise. Further advice on quality audits and their application has been published by the NHS Pharmaceutical Quality Control Committee (*NHS Pharmaceutical Quality Control Committee (1999). Quality Audits and Their Application to Hospital Pharmacy Technical Services. Norwich, NHS Pharmaceutical Quality Control Committee*)

In addition to the regulatory aspects of audit as outlined above, the British Nuclear Medicine Society (BNMS) can undertake invited organizational audits of nuclear medicine departments. This process includes the radiopharmacy, and looks at all aspects of the practice of radiopharmacy both within the unit itself and its relationship and interaction with the wider department *(A mechanism for professional and organizational audit of radiopharmacy departments. Cox JA, Hesslewood SR and Palmer AM. Nuclear Medicine Communications (1994) 15, 890-898).* The BNMS Radiopharmacy audit tool examines radiation safety, as well as GMP, as it applies to Radiopharmacy.

Case study 3:
Finished Product Testing and Quality Assurance

Radiochemical Purity (RCP) Analysis Failure

Rationale for performing the test Manufacture of radiopharmaceuticals involves the creation of a new chemical entity, and radiochemical purity testing also gives assurance that the manufacturing operation is capable of consistently producing products which are suitably radio-labelled. This is not required for every batch prepared; Purpose: to investigate any unusual biodistributions.

Possible causes of a failure Genuine fail of binding of technetium to diagnostic imaging agent (ie failure of radiolabelling procedure); operator error (in performing RCP test); using unvalidated or incorrect method; using incorrect materials; using inappropriate equipment.

Suggested actions Follow the Out of Specification (OOS) procedure. This is likely to include repeating the test – but be careful you aren't 'testing to pass'; if future tests pass, assurance that the result is correct can be gained by reviewing scans to determine whether the biodistribution is unusual; review test results for other kits from same batch; review method in manufacturer's SmPC; review materials – including expiry; review equipment, eg are proper tanks used?; review operator technique, e.g. are they touching the strips?; refresh operator training; review how chromatography strips are assayed. If the test result is a release criterion, an OOS procedure must be in place which must be followed in this instance.

Impact of failure Low radiochemical purity could result in a poor quality image, and in the worst case scenario, in inaccurate diagnostic information or repeat radiation exposure. If the failure is confirmed, the Nuclear Medicine staff / Nuclear Medicine Clinician or Radiologist should be informed. An investigation in line with the local Out of Specification results procedure should be carried out, with root cause analysis an appropriate corrective and preventative actions being put in place.