Medicinal chemistry I

Research and development of new drugs,
Legislational requirements for investigational drugs,
Requirements for manufacturing of substances,
Good Manufacturing Practice

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Medicinal chemistry I

- Research and development of Active Pharmaceutical Ingredients (API)
  - Research
    - new chemical entities, synthesis and evaluation of numbers of substances
  - Development
    - selected compound
    - aimed to introducing into clinical practice
  - Legislation regarding API
    - efficacy
    - safety
    - quality
- Manufacturing of API
    - Principles of Good Manufacturing Practice (GMP)

Strategy of drugs research and development (R&D)

- Basic research
  - Serendipitous discovery
    - peniciline
    - cisplatin
    - sildenafil
  - broad screening of new or known compounds
    - screening of efficacy of known compounds
  - research based on knowledge of structure-effect relationship
    - synthesis
      - homologous series
      - positional isomerism
      - izosteric substitutions
    - mathematical models

Patent protection

- Purpose is protection of drug originators.
- The best option is covering of structure of API – usually the first patent application.
- The patent protection is usually extended by patents regarding particular steps of synthesis, specific drug properties (polymorphism), dosage forms … etc.
- The basic duration of patent protection is 20 years. It can be prolonged at some specific conditions.
- Patent application ≠ granted patent
  - novelty
  - inventive step
  - industrial application

Patents

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New drug development

- Development of selected compounds
  - biological evaluation
    - efficacy
    - toxicity
  - synthesis optimalisation, development of manufacturing process
    - legislation requirements regarding quality
  - clinical evaluation
    - three phases of clinical evaluation
  - dosage form development

New drug development

- Efficacy
  - evidence of pharmacological effect, which have to be significantly better in comparison with clinically used drugs
- Safety
  - Acute toxicity – single dose toxicity, LD_{50} determination was abandoned (ethical reasons). MTD (maximum tolerated dose) is used
  - Repeated dose toxicity – duration of theese studies is dependent on intended dosage schedule
  - Safety pharmacology
    - influence on cardiovascular system
    - influence on CNS
    - GIT toxicity (emetogennic effect – anticancer drugs)
- Quality
  - Requirements for qualitative parameters of API, needed for first administration to patients

New drug development – legislation

- Czech Republic
  - Act 378/2004 Sb. „Drug act“
    - Regulation 86/2008 Good laboratory practice
    - Regulation 226/2008 Good clinical practice
  - Guidelines SÚKL – State institure for drug control – http://www.sukl.cz/
    - VYR 32 rev.2 annex 13 manufacturing of investigational drugs
    - VYR 26 Guidance of Good manufacturing practice for API
    - KLH-12 – Requirements of GMP certificate before start of clinical evaluation
    - KLH-19 – Application for clinical evaluation

New drug development – legislation (EU)

- EudraLex – legislation of European union
  - http://ec.europa.eu/health/documents/eudralex/index_en.htm
- Regulations
  - Regulations are the most direct form of EU law - as soon as they are passed, they have binding legal force throughout every Member State, on a par with national laws. National governments do not have to take action themselves to implement EU regulations.
- Directives
  - EU directives lay down certain end results that must be achieved in every Member State. National authorities have to adapt their laws to meet these goals, but are free to decide how to do so. Directives may concern one or more Member States, or all of them.
- European Medicines Agency (EMA)
  - Guidelines of EMEA are published on internet: http://www.ema.europa.eu/ema/
  - They have similar structure as the ICH guidelines.

New drug development – legislation (USA)

- Code of Federal Regulations Title 21 – *Federal Food, Drug, and Cosmetic Act*
  - 21 CFR Part 209–211 – principles of Good Manufacturing Practice
    - http://cfr.regstoday.com/21cfr.aspx
    - violation of GMP principles is in USA violation of federal act
- **F**ood and **D**rug **A**dministration
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - Guidances, guidance for industry – guidance documents represent the Agency's current thinking on a particular subject.
  - An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

New drug development – legislation (ICH)

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
  - Fulltexts of all guidances are at http://www.ich.org.
  - The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration.Tge guidances are structured into parts *Quality*, *Safety*, *Efficacy* a *Multidisciplinary*.
  - Particular guidances are implemented in national legislation systems

New drug development – legislation (ICH)

- Quality
  - Stability
  - Analytical validation
  - Impurities
  - Pharmacopoeias
  - Quality of Biotechnological Products
  - Specifications
  - Good Manufacturing Practice (API)
  - Pharmaceutical development
  - Quality Risk Management
  - Pharmaceutical Quality Systém
  - Development and Manufacturing of Drug Substances

New drug development – legislation (ICH)

- Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances*
  - A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.
    - development of reproducible and apropriate analytical methods for determination of the API and impurities (incl. decomposition products).
    - development of methods for deteminatiuon of relevant solvents
    - Other methods for determination of other physico-chemical characteristics of the API (particle size, polymorphism, microbiological contamination etc.)
    - **Determination of limits for all parameters chosen**
- API specification at the start of clinical evaluation has to be almost the same, as the specification for manufacturing of marketed drug.

New drug development – legislation (ICH)

- Analytical specification
  - Description
    - a qualitative statement about the state (e.g. solid, liquid) and color
  - Identification
    - Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy.
  - Assay
    - A specific procedure to determine the content of the new drug substance.
  - Impurities
    - Organic and inorganic impurities and residual solvents are included in this category.
  - Specific tests
    - Physicochemical properties, Particle size, Polymorphic forms, Microbial limits, etc…

New drug development – legislation (ICH)

- Stability
  - The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.
  - Data from formal stability studies should be provided on at least three primary batches of the drug substance.
  - Stress tests
    - first stability studies, influence of temprature, humidity, pH, oxidation and reductive species
  - Basic types of stability testing
    - Long-term 25/30°C ± 2°C/60% RH ± 5% RH, min. 12 months
    - Intermediate 30°C ± 2°C/65% RH ± 5% RH, min. 6 months
    - Accelerated 40°C ± 2°C/75% RH ± 5% RH, min. 6 months

New drug development – legislation (ICH)

- Q3A(R2): *Impurities in New Drug Substances*
  - Clasification, identification, impurities in specifications, analytical methods
    - starting materials, intermediates of chemical synthesis, decomposition products, catalysators, inorganic compounds, …
    - residual solvents (Q3C(R3): *Impurities: Guideline for Residual Solvents*)
  - Safety
    - toxicity of impurities based on their content in the API
  - Limits of impurities

Maximal daily dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2g/day	0.05 %	0.1% or 1.0 mg/day	0.15% or 1.0 mg/day
> 2g/day	0.03 %	0.05 %	0,05 %

» Qualification – toxicological study

New drug development – legislation (ICH)

- Q3C(R5): *Impurities: Guideline for Residual Solvents*
  - Methods for determination of residual solvents, requirements for analytical methods and limits
  - Classification and limits
    - *Class I* – Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
      - benzene, tetrachlormethane, 1,2-dichlorethane, 1,1-dichlorethene, 1,1,1,-Trichlorethane
    - *Class II* – Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
      - ie. acetonitrile, chloroform, dimethylformamide, methanol, toluene, xylene
    - *Class III* – Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

New drug development – preclinical evaluation

- Efficacy
  - based on intended indication class *in vitro* and *in vivo* evaluation
  - *In vitro* evaluation
    - chemotherapeutics, anticancer drugs – there is possibility of use of cell cultures
  - *In vivo* efficacy
    - all studies in animals must be approved by ethical commitees and provided only on certified sites
    - animal models of some disseases
    - tumour xenografts

New drug development – legislation (ICH)

- Safety
  - Carcinogenicity Studies
  - Genotoxicity Studies
  - Toxicokinetics and Pharmacokinetics
  - Toxicity Testing
  - Reproductive Toxicology
  - Biotechnological Products
  - Pharmacology Studies
  - Immunotoxicology Studies

New drug development – ICH – Safety

- Safety
  - Toxicity (different species – rodent vs. non-rodent)
    - acute (single-dose) – MTD
    - repeated dose toxicity – MTD, specific toxicity
    - imunotoxicity
    - mutagenicity, carcinogenicity
  - Safety pharmacology
    - kardiovascular system
    - influence on CNS
    - other specific tests (emetogenic effect)
- Toxicokinetics and pharmacokinetics
  - Determination of basic PK parameters and theis relationship with toxicity, comparison of different animal species
  - Requirement of Good Laboratory Practice (GLP) conditions during theese studies

Good Laboratory Practice

- OECD principles of Good Laboratory Practice
  - Used mostly during animal studies
  - GLP certification is needed for analytical laboratories, which evaluate samples from toxicokinetic and pharmacokinetic studies
- Principles
  - Test Facility Organisation and Personnel
  - Facilities
  - Quality Assurance Programme
  - Apparatus, Material, and Reagents
  - Performance of the Study
  - Reporting of Study Results

New drug development – legislation (ICH)

- Efficacy
  - Clinical Safety
  - Clinical Study Reports
  - Dose-Response Studies
  - Ethnic Factors
  - Good Clinical Practice
  - Clinical Trials
  - Guidelines for Clinical Evaluation by Therapeutic Category
  - Pharmacogenomics

New drug development – clinical evaluation

- Phase I – Human Pharmacology
  - Study aims
    - MTD determination
    - dose-limitting toxicity determination
    - basic side effect determination
    - determination of basic pharmacokinetic parameters
    - efficacy – optional
  - Study design
    - usually on health volunteers
      - not applicable in cytotoxic anticancer drugs – patients in terminal stage if dissease are required
    - dose escalation study
      - dose escalation by 100, 50, 33, 25% and 25 % of previous dose
    - the end of a study is at maximum tolerated dose or in case of non-linear pharmacokinetics
    - at particular doses is evaluated toxicity and PK (optionally efficacy)

New drug development – clinical evaluation

- Phase II – Therapeutic Exploratory
  - Study aims
    - Efficacy of the drug at different dose schedules
    - In oncology – finding of indication area
    - Establish safety profile
    - Pharmacokinetics
    - Adverse effects
  - Study design
    - Patients with relevant disease
    - Multiple studies
    - Multi-site studies
    - Dose-response exploration studies

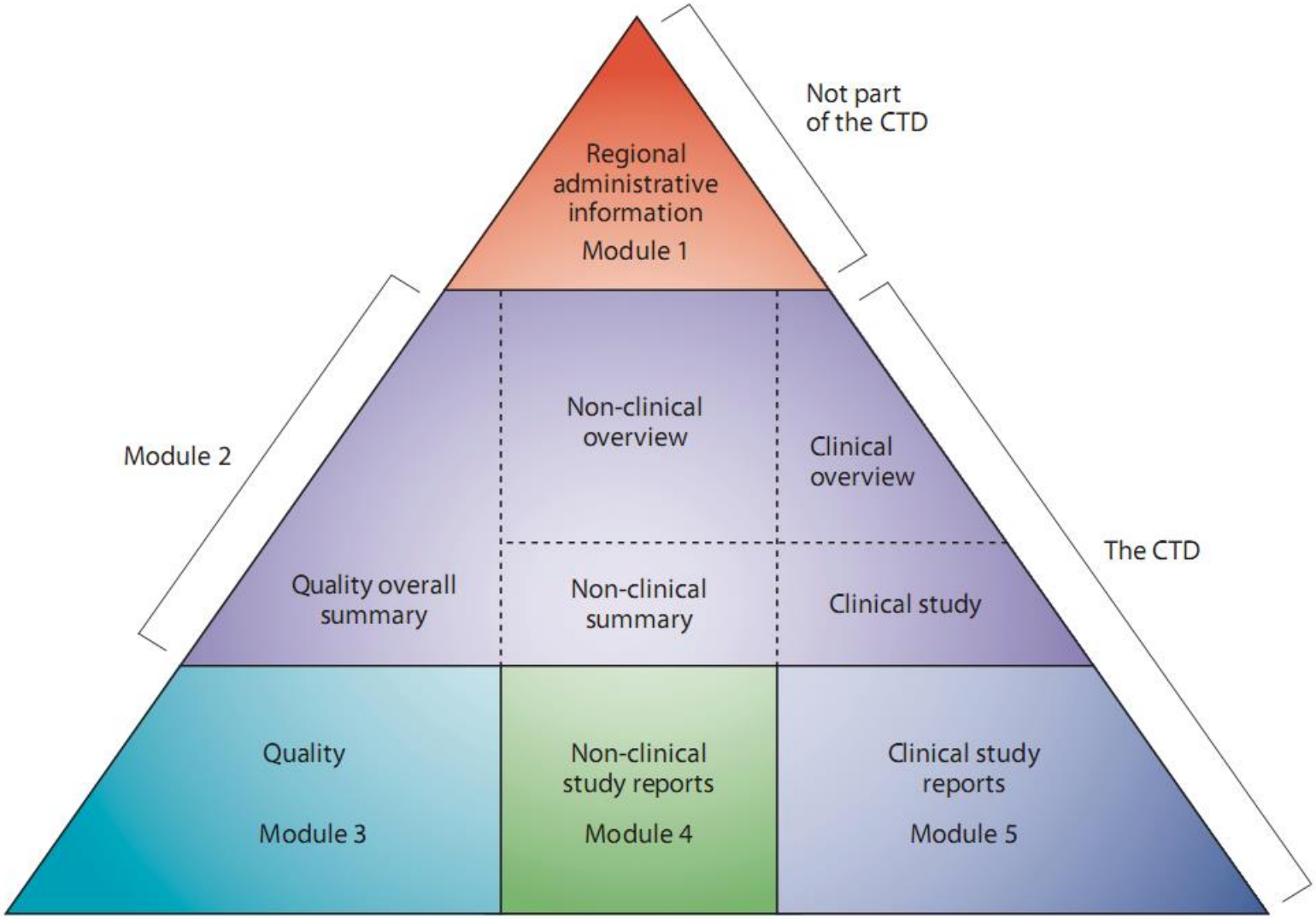
New drug development – clinical evaluation

- Phase III – Therapeutic Confirmatory
  - Study aims
    - Demonstrate/confirm efficacy
    - Provide an adequate basis for assessing the benefit/risk relationship to support licensing
    - Establish dose-response relationship
  - Study design
    - Adequate, and well controlled studies to establish efficacy
    - Randomised, placebo-controlled, double-blinded study
    - multicentric studies – 1000 and more patients

New drug development – legislation (ICH)

- Common Technical Document (CTD)
  - The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionised the regulatory review processes, led to harmonised electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.
  - The CTD is organised into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA.

New drug development – legislation (ICH)



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

New drug development – quality of API

- API quality
  - structure – specific evidence of the structure by at least two methods (X-ray, NMR, IR, MS)
  - physico-chemical characteristics (melting/boiling point, solubility in different solvents)
  - information regarding stability (min 6 months at normal storage conditions)
  - detailed descriprion of all synthetic steps
  - purity of the API, with actual results of analysis includind analytical methods
- Manufacturing in GMP regime
  - certificate of GMP for the particular process
  - inspection of state authority of the manufacturing site
  - in case of investigational drugs are some exceptions in comparison with manufacturing of registered drugs

Good Manufacturing Practice

- According GMP principles shoul be provided manufacturing of all substances, intended for human or veterinary use, including administration during all phases of clinical evaluation.
- ICH Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients.
  - fulltext at http://www.ich.org
  - This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18.

Good Manufacturing Practice

- In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls.
- In this Guide the term "**should**" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

Good Manufacturing Practice

- Quality assurance unit
  - The quality unit(s) should review and approve all appropriate quality-related documents.
  - Releasing or rejecting all APIs.
  - Making sure that internal audits (self-inspections) are performed
  - Approving changes that potentially impact intermediate or API quality
  - Making sure that critical deviations are investigated and resolved
  - Approving changes that potentially impact intermediate or API quality
  - Making sure that effective systems are used for maintaining and calibrating critical equipment

Good Manufacturing Practice

- Personnel
  - There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.
  - The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.
  - There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.
  - Personnel should practice good sanitation and health habits.
  - Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions.

Good Manufacturing Practice

- Buldings and facilities
  - Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.
  - The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.
  - Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.
  - Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Good Manufacturing Practice

- Process equipment
  - Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.
  - Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter their quality.
  - Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production should be appropriately identified.
  - Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture.
  - Equipment should be identified as to its contents and its cleanliness status by appropriate means.
  - Instruments that do not meet calibration criteria should not be used.

Good Manufacturing Practice – Documentation

- All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.
- A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.
- All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

Good Manufacturing Practice – Documentation

- When entries are made in records, these should be made *indelibly* in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and *leave the original entry still readable*.
- Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.
- Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

Good Manufacturing Practice – Documentation

- Standard Operating Procedure (SOP)
  - written instruction for usage and maintenance of all relevant equipment
  - applicabble also for routine procedures (sampling, weighing …)
  - every SOP must be approved by quality assurance unit
  - SOP must be placed at the equipment
  - all equipment with SOP have a logbook
    - records of use
    - records of maintenance

Good Manufacturing Practice – Documentation

- Master Production Instructions
  - The name of the intermediate or API being manufactured,
  - A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics,
  - An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included.,
  - The production location and major production equipment to be used,
  - Detailed production instructions, including the:
    - » sequences to be followed,
    - » ranges of process parameters to be used,
    - » sampling instructions and in-process controls with their acceptance criteria, where appropriate,
    - » time limits for completion of individual processing steps and/or the total process, where appropriate,
    - » expected yield ranges at appropriate phases of processing or time,
    - » The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

Good Manufacturing Practice – Documentation

- Batch
  - A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.
  - *Batch production records* should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch.
  - These records should be numbered with a unique batch or identification number, dated and signed when issued.

Good Manufacturing Practice – Documentation

- Batch record
  - Dates and, when appropriate, times,
  - Identity of major equipment used
  - Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing,
  - Actual results recorded for critical process parameters,
  - Any sampling performed,
  - Signatures of the persons performing and directly supervising or checking each critical step in the operation,
  - In-process and laboratory test results,
  - Actual yield at appropriate phases or times,
  - Description of packaging and label for intermediate or API,
  - Representative label of API or intermediate if made commercially available,
  - Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
  - Results of release testing.

Good Manufacturing Practice – Materials management

- There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.
- Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.
- At least one test to verify the identity of each batch of material should be conducted. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.
  - Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained.
- Samples should be representative of the batch of material from which they are taken.

Good Manufacturing Practice – Production

- Production operations
  - Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.
  - If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available
  - Actual yields should be compared with expected yields at designated steps in the production process.
  - *Any deviation should be documented and explained*. Any critical deviation should be investigated.
  - Intermediates, stored for further processing should be stored at conditions necessary for their sufficient stability

Good Manufacturing Practice – Production

- In-process controls
  - Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
  - Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).
  - In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Good Manufacturing Practice – Production

- Batches blending
  - Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications.
    - Blending of small batches to increase batch size
    - Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.
  - The batch record of the blending process should allow traceability back to the individual batches that make up the blend.
  - If the blending could adversely affect stability, stability testing of the final blended batches should be performed.
  - The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

Good Manufacturing Practice

- Packaging and labelling
  - There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.
  - Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.
- Warehousing procedures
  - Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.
- Distribution procedures
  - APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit.
  - APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Good Manufacturing Practice – laboratory controls

- General controls
  - There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data.
  - Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process.
    - control of the impurities
    - microbiological purity.
    - endotoxins assay.
  - Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

Good Manufacturing Practice – laboratory controls

- General controls
  - Any out-of-specification result obtained should be investigated and documented according to a procedure.
    - analysis of the data, assessment of whether a significant problem exists.
    - corrective actions.
    - Any resampling and/or retesting after OOS results should be performed according to a documented procedure.
  - **Primary reference standards**
    - The source of each primary reference standard should be documented.
    - Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations.
  - Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established
    - Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Good Manufacturing Practice – laboratory controls

- Certificate of analysis
  - Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.
  - The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).
  - Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer.

Good Manufacturing Practice – laboratory controls

- Stability monitoring
  - A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.
  - The test procedures used in stability testing should be validated and be stability indicating.
  - Stability samples should be stored in containers that simulate the market container.
  - Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date.
  - Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.
  - ICH guidelines regarding stability

Good Manufacturing Practice – laboratory controls

- Retention samples
  - The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.
  - Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer.
  - The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system.
  - Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

Good Manufacturing Practice – Validation

- Validation policy
  - The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:
    - Defining the API in terms of its critical product attributes,
    - Identifying process parameters that could affect the critical quality attributes of the API,
    - Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.
  - Validation should extend to those operations determined to be critical to the quality and purity of the API.

Good Manufacturing Practice – Validation

- Validation protocol and report
  - *Validation protocol* approved detailed plan of validation
  - *Validation report* should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.
  - Any variations from the validation protocol should be documented with appropriate justification.
- Qualification
  - *Design Qualification* (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
  - *Installation Qualification* (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
  - *Operational Qualification* (OQ): documented verification that the equipment or systems, as installed, perform as intended throughout the anticipated operating ranges.
  - *Performance Qualification* (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

Good Manufacturing Practice – Validation

- Process validation
  - Process Validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.
  - There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used.
    - *Prospective validation* performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.
    - *Concurrent validation* can be conducted when only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified.

Good Manufacturing Practice – Validation

- Cleaning validation
  - Cleaning procedures should normally be validated.
  - Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues.
  - Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production.
  - Validated analytical methods having sensitivity to detect residues or contaminants should be used.
  - Residue limits should be practical, achievable, verifiable and based on the most deleterious residue.
  - The method's attainable recovery level should be established.

Good Manufacturing Practice – Validation

- Validation of analytical methods
  - Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference.
  - The suitability of *all* testing methods used should nonetheless be verified under actual conditions of use and documented.
  - ICH guidelines for validation of analytical methods
  - Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

Good Manufacturing Practice – Change control

- A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
- Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.
  - Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impact on the process.
- When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

Good Manufacturing Practice

- Rejection and re-use of materials
  - Rejection
    - Intermediates and APIs failing to meet established specifications should be identified as such and quarantined
  - Reprocessing
    - Introducing of products that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps is generally considered acceptable.
  - Recovery of materials and solvents
    - Well documented
    - Apropriate laboratory controls
  - Returns
    - Returned intermediates or APIs should be identified as such and quarantined

Good Manufacturing Practice

- Complaints and recalls
  - written procedures, documented
- Contract manufacturers (incl. laboratories)
  - All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- Specific guidances for APIs manufactured by cell/culture fermentation

Good Manufacturing Practice

- APIs for use in clinical trials
  - The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API.
  - Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages.
  - Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.
  - The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

Good Manufacturing Practice

- APIs for use in clinical trials
  - Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.
  - Process validation for the production of APIs for use in clinical trials is normally inappropriate.
  - Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.
  - While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.
  - A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

Summary

- Basic research
- Development
  - legislation requirements
  - preclinical
  - clinical
  - substance quality requirements
- Good Manufacturing Practice
  - Documentation, Documentation, Documentation, Documentation, …
    - Procedures
    - Records
  - APIs for clinical evaluation have to meet almost the same qualitative requirements as the commercially produced substances