NIRMALA COLLEGE OF PHARMACY
MUVATTUPUZHA

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FIRST CYCLE NAAC ACCREDITATION 2023

CRITERION 1

CURRICULAR ASPECTS

1.2.2 Percentage of students enrolled in Certificate/ Add-on/Value added programs and also completed online MOOC programs like SWAYAM, NPTEL etc. as against the total number of students during the last five years

Submitted to

THE NATIONAL ASSESSMENT AND ACCREDITATION COUNCIL

1.2.2. Number of students enrolled in subject related Certificate/ Add-on/Value added programs and also completed online MOOC programs like SWAYAM, NPTEL etc. year wise during last five year

STUDY MATERIAS OF ADD-ON COURSE OFFERED BY THE INSTITUTION

Sl. No	COURSES	View Page
1.	Advanced Computational Drug Design	View Page
2.	Advanced Computational Biochemistry	View Page
3.	Value Creation Through Innovation	View Page
4.	Clinical Skill Enrichment Programm	View Page
5.	Communicative English	View Page
6.	Quality By Design Setting of Qualitative Targets	View Page
7.	Sigma Plot: A Tool for Statistical Analysis	View Page
8.	Pharmacokinetic Modelling Programme	View Page
9.	Basic Course in Yoga and Meditation	View Page

Computer aided drug design

By Dr Sameh Ahmad M- Abdelghany

Section 01

Basic Drug designing

Drug Design

- is the inventive process of finding new medications based on the knowledge of a biological target.
- It involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it.

Life Cylce of Drug Design

❖ **Traditional Life Cycle**

Modern Drug Design

Target Selection

- Identification of Target
- Verification of target
- Target Selection

Lead Identificatio n

- Screen Development
- High throughput screening
- Secondary assay

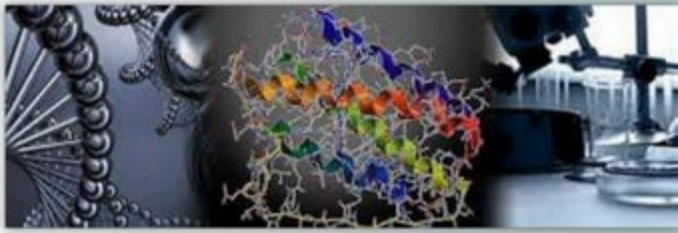
Lead Optimization

- Lead explosion
- Potency in disease
- Pharmacokinetics

Final

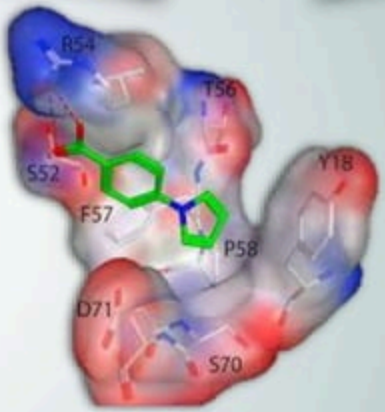
Drug Designing…

- Selected/designed molecule should be:
  - Organic small molecule.
  - Complementary in shape to the target.
  - Oppositely charge to the biomolecular target .



Drug Designing…

- This molecule will:
  - interact with target
  - bind to the target
  - activates or inhibits the function of a biomolecule such as a protein

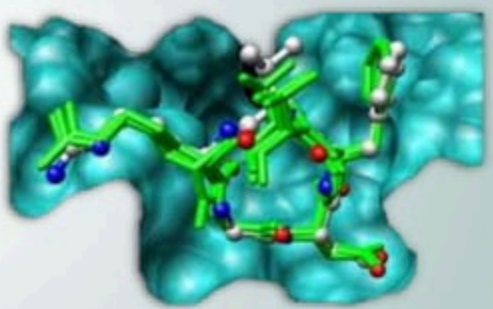


Drug Designing…

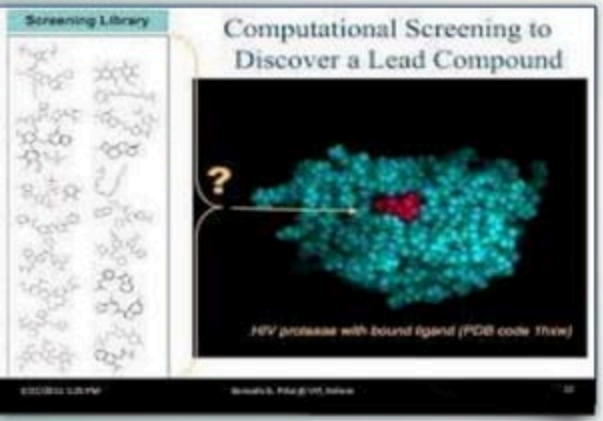
- Drug design frequently but not necessarily relies on computer modeling techniques.
- This type of modeling is sometimes referred to as computer-aided drug design.

Mechanism based drug design

- When the disease process is understood at the molecular level and the target molecule(s) are defined, drugs can be designed specifically to interact with the target molecule in such a way as to disrupt the disease.



Computer-aided drug design(CADD)



- CADD represents computational methods and resources that are used to facilitate the design and discovery of new therapeutic solutions.

Introduction to CADD

- Drug design with the help of computers may be used at any of the following stages of drug discovery:
- hit identification using virtual screening (structure- or ligand-based design)
- hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
- lead optimization: optimization of other pharmaceutical properties while maintaining affinity.

Objective of CADD

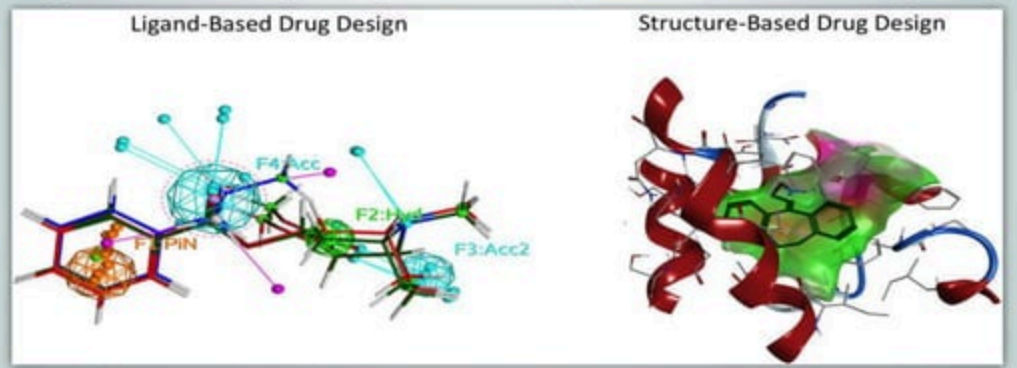
- To change from:
  - Random screening against disease assays
  - Natural products, synthetic chemicals

- To:
  - Rational drug design and testing
  - Speed-up screening process
  - Efficient screening (focused, target directed)
  - De novo design (target directed)
  - Integration of testing into design process
  - Fail drugs fast (remove hopeless ones as early as possible)

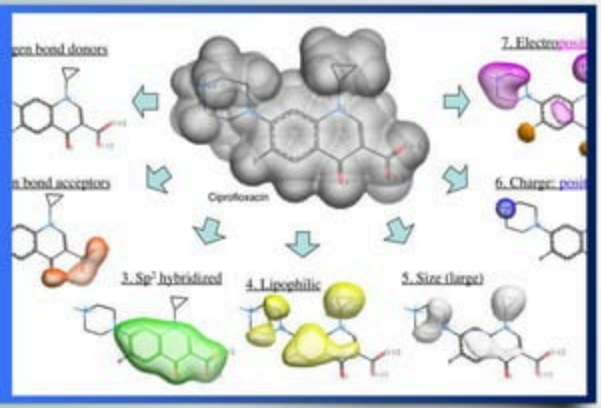
Types of drug design

1) Ligand based drug design

2)Structure based drug design



Ligand-based drug design

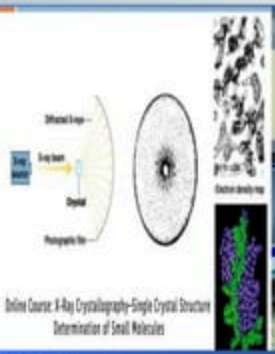


- relies on knowledge of other molecules that bind to the biological target of interest.
- used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.

Ligand-based drug design

- a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target.
- Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs.

Structure-based drug design:



X-ray crystallography

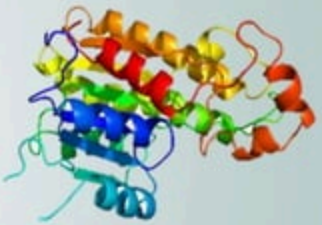
NMR spectroscopy

- relies on knowledge of the three dimensional structure of the biological target obtained through :

1. x-ray crystallography
2. NuclearMagnetic Resonance (NMR) spectroscopy.

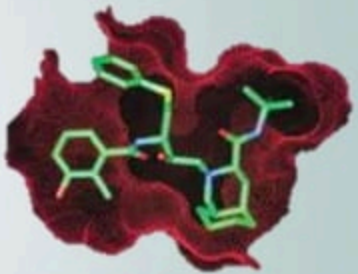
Structure-based drug design

- If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein.
- Homology modeling, also known as comparative modeling of protein, refers to constructing an atomic-resolution model of the "target" and an experimental three-dimensional structure of a related homologous protein (the "template").



Structure-based drug design

- Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using:
- interactive graphics
- Intelligence of a medicinal chemist.
- various automated computational procedures may be used to suggest new drug candidates.



Methods

1) **Virtual screening :**

- The first method is identification of new ligands for a given receptor by searching large databases of 3D structures of small molecules to find those fitting the binding pocket of the receptor using fast approximate docking programs.

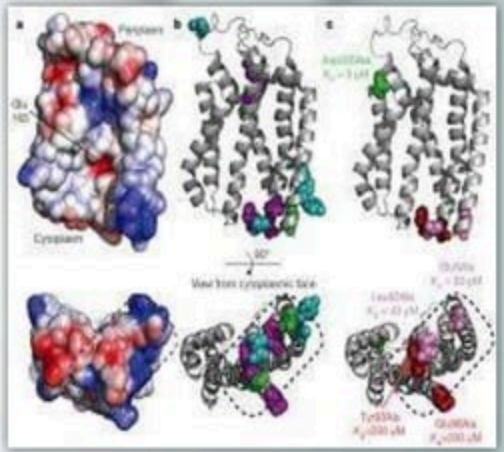
2) **de novo design of new ligands:**

- In this method, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures can be suggested.

3) **optimization of known ligands** by evaluating proposed analogs within the binding cavity.

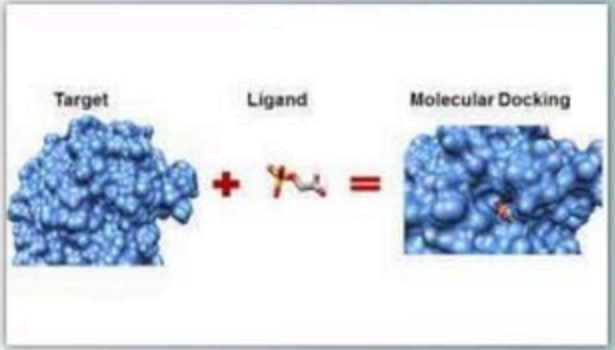
Binding site identification

- It is the first step in structure based design.
- relies on identification of concave surfaces on the protein that can accommodate drug sized molecules that also possess appropriate "hot spots" (hydrophobic surfaces, hydrogen bonding sites, etc.) that drive ligand binding.



Docking & Scoring

- Docking attempts to find the "best" matching between two molecules
- It includes finding the Right Key for the Lock
- To place a ligand (small molecule) into the binding site of a receptor in the manners appropriate for optimal interactions with a receptor.
- To evaluate the ligand-receptor interactions in a way that may discriminate the experimentally observed mode from others and estimate the binding affinity.



Components of Docking

I- **pre- and/or during docking**:

- Representation of receptor binding site and ligand

II- **during docking**:

- Sampling of configuration space of the ligand-receptor complex

III- **during docking and scoring**:

- Evaluation of ligand-receptor interactions

Advantages of CADD

- Time
- Cost
- Accuracy
- information about the disease
- screening is reduced
- Database screening
- less manpower is required

Success stories of CADD

- K+ ion channel blocker
  - structural based discovery

- Ca2+ antagonist / T-channel blocker
  - chemical descriptor based discovery

Success stories of CADD

- Glyceraldehyde-phosphate DH inhibitors (anti-trypanosomatid drugs)
  - combinatorial docking

- Thrombin inhibitor
  - docking, de-novo design

Section 02

Computational Tools For Drug Designing

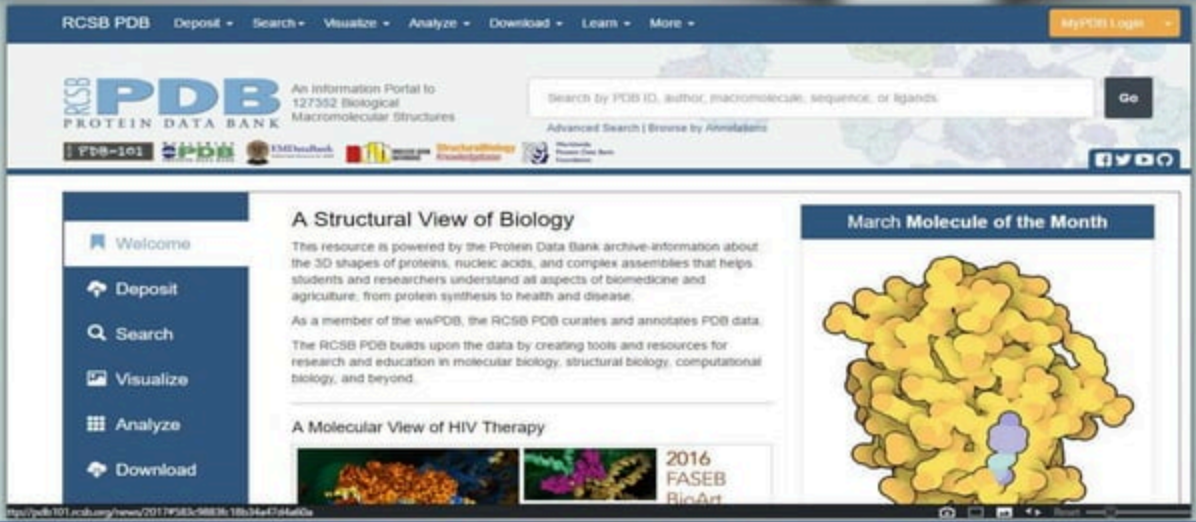
Categories of software

1. Databases & Draw Tools
2. Molecular Modeling & Homology Modeling
3. Binding site prediction & Docking
4. Ligand design Screening -QSAR
5. Binding free energy estimation
6. ADME Toxicity

Databases

- ZincDatabase, Zinc15Database
- ChEMBL
- JChemforExcel
- ProteinDataBank(PDB)
- BindingMOAD(MotherOfAllDatabase)
- PDBbind
- STITCH,SMPDB

Databases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A Structural View of Biology
This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.
As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.
The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.
A Molecular View of HIV Therapy
2016
FASEB
March Molecule of the Month

Databases

UCSF University of California, San Francisco | About UCSF | Search UCSF | UCSF Medical Center

Shoichet Laboratory docking.org

ZINC 12

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Active cart: Temporary Cart (0 items)

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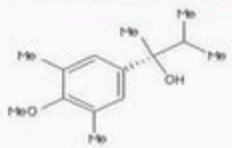
Please consider switching to ZINC15, which is superior to ZINC12 in most ways. If you prefer ZINC12 after trying ZINC15, we would like to know why @chem4biology so that we can get you to make the switch.

Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 35 million purchasable compounds in ready-to-dock, 3D formats. ZINC is provided by the Irwin and Shoichet Laboratories in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). To cite ZINC, please reference: Irwin, Sterling, Mysinger, Bolstad and Coleman, *J. Chem. Inf. Model.* 2012 DOI: 10.1021/ci3001277. The original publication is Irwin and Shoichet, *J. Chem. Inf. Model.* 2005;45(1):177-82 PDF, DOI. We thank NIGMS for financial support (GM71896).

ZINC ID, Drug Name, SMILES, Catalog, Vendor Code, Target & mo Go

Structure/Draw Physical Properties Catalogs & Vendors ZINC IDS Targets Rings Combination

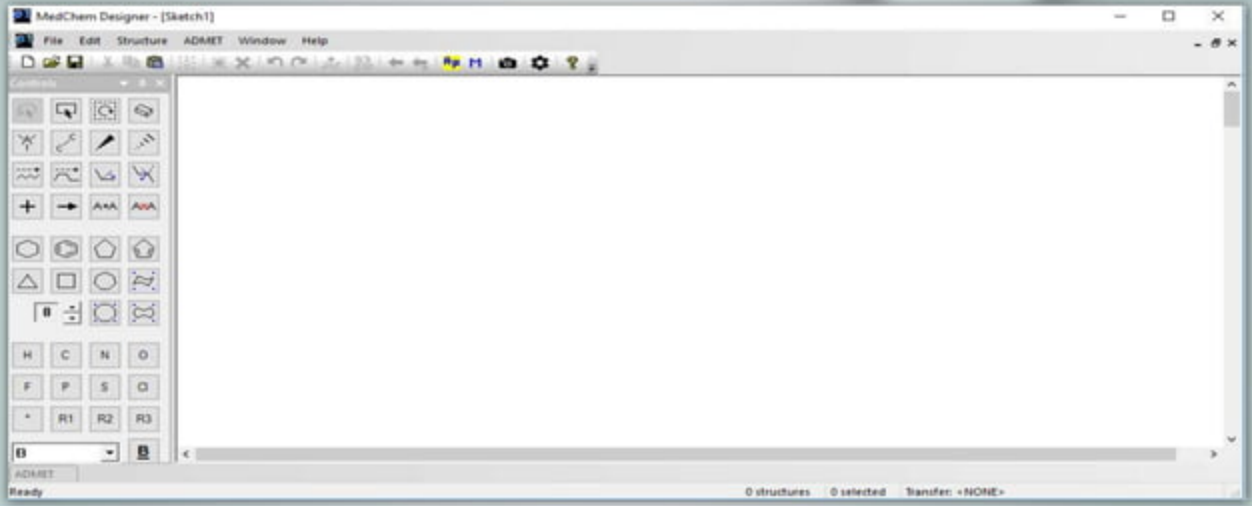
Molecule of the Minute 95739237



Draw Tools

- ChemDraw
- MarvinSketch
- ACD/ChemSketch
- Marvin molecule editor and viewer
- ChemWriter
- UCSFChimera
- Pymol

Medchem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F P S Cl
R1 R2 R3
ADMET
Ready
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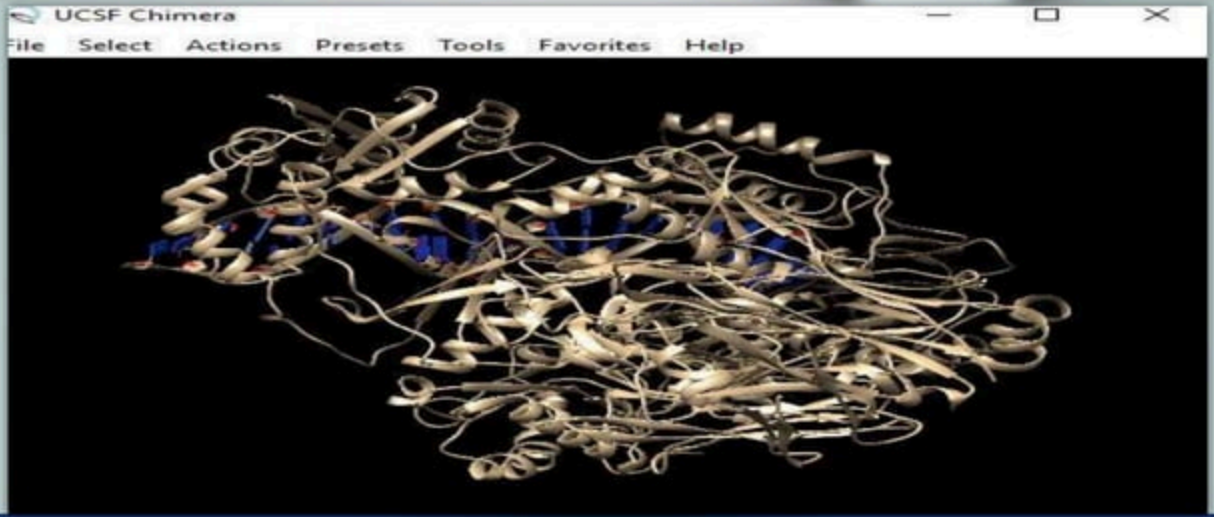
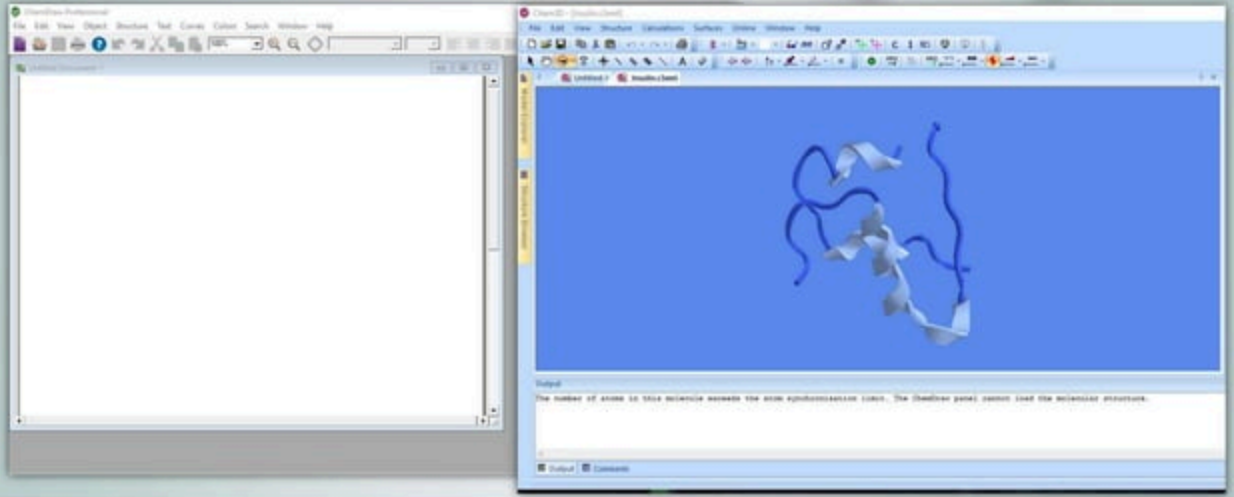
UCSF Chimera



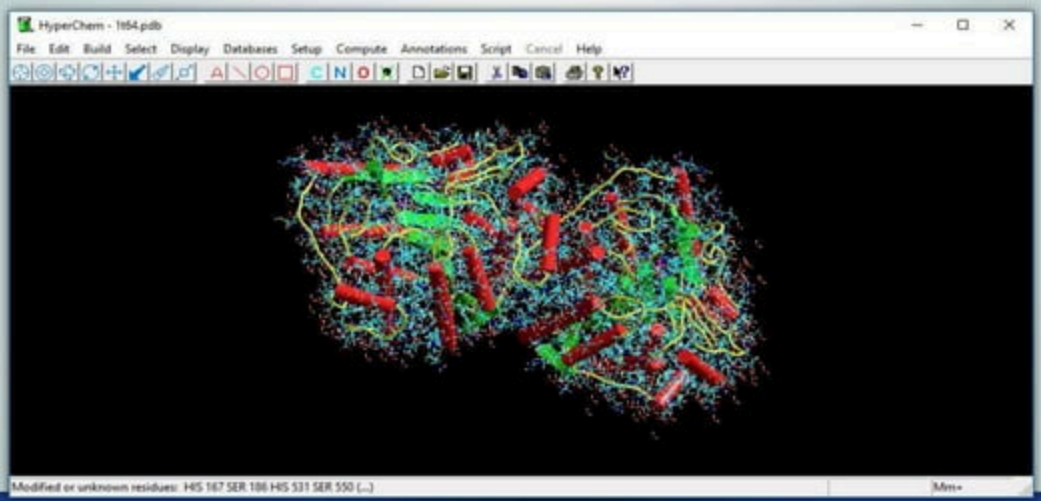
Chem Office



Molecular Modeling

- CHARMM
- GROMACS
- Amber
- SwissParam
- CHARMM-GUI
- CHARMMing.org
- SwissSideChain

Hyperchem


HyperChem - 1t64.pdb
File Edit Build Select Display Databases Setup Compute Annotations Script Cancel Help
Modified or unknown residues: HIS 167 SER 186 HIS 531 SER 550 (...)
Mm+

Homology Modeling

- Modeller
- I-TASSER
- LOMETS
- SWISS-MODEL
- SWISS-MODELRepository
- Robetta

LOMETS

LOMETS (LOcal MEta-Threading-Server) results for test

>test, contains 298 residues, "easy" target

Predicted Secondary Structure (by PSI-PRED)

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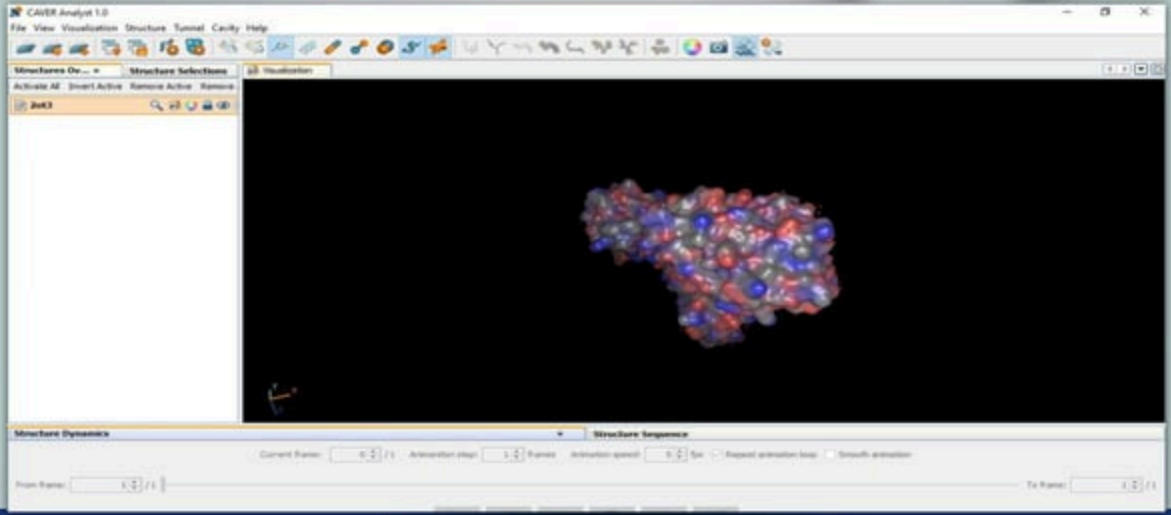
For detailed information about output, please see readme file

Binding site prediction

- MED-SuMo
- CAVER
- FINDSITE
- sc-PDB
- Pocketome
- PocketAnnotatedatabase
- 3DLigandSite,
- metaPocket
- PocketAnnotate

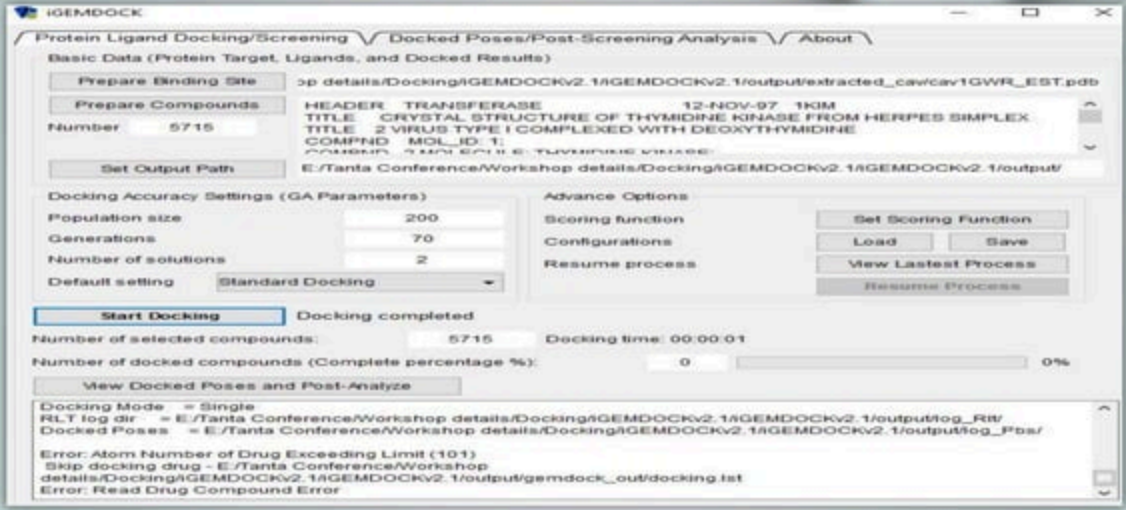
CAVER


CAVER Analyst 1.0
File View Visualization Structure Tunnel Cavity Help
Structures Ov...
Structure Selections
Activate All Invert Active Remove Active Remove
2ot3
Visualization
Structure Dynamics
Structure Sequence

Docking

- Autodock
- DOCK
- GOLD
- SwissDock
- DockingServer
- 1-ClickDocking
- iGemdock

iGemdock


iGEMDOCK
Protein Ligand Docking/Screening
Docked Poses/Post-Screening Analysis
About
Basic Data (Protein Target, Ligands, and Docked Results)
Prepare Binding Site
Prepare Compounds
Number 5715
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TITLE CRYSTAL STRUCTURE OF THYMIDINE KINASE FROM HERPES SIMPLEX
TITLE 2 VIRUS TYPE I COMPLEXED WITH DEOXYTHYMIDINE
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Docking Accuracy Settings (GA Parameters)
Population size 200
Generations 70
Number of solutions 2
Default setting Standard Docking
Advance Options
Scoring function
Set Scoring Function
Configurations
Load
Save
Resume process
View Lastest Process
Resume Process
Start Docking
Docking completed
Number of selected compounds: 5715
Docking time: 00:00:01
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View Docked Poses and Post-Analyze
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Error: Read Drug Compound Error

Screening

- Pharmer
- Catalyst
- PharmaGist
- SwissSimilarity
- Blaster
- AnchorQuery
- ligandscout
- Discovery Studio

Discovery Studio

Target prediction

- MolScore-Antivirals
- MolScore-Antibiotics
- Swiss Target Prediction
- SEA
- ChemProt

Ligand design

- GANDI
- LUDI
- AutoT&T2
- SwissBioisostere
- VAMMPIRE
- sc-PDB-Frag
- e-LEA3D
- eDesign
- iScreen

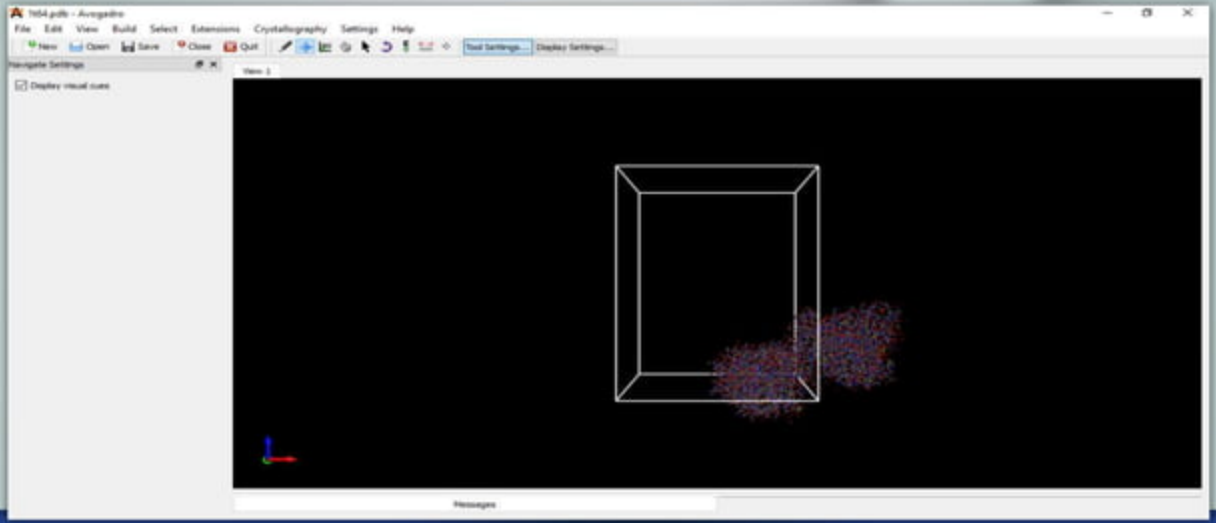
Binding free energy estimation

- Hyde, X-score
- NNScore
- DSXONLINE
- BAPPLserver
- BAPPL-Zserver,

QSAR

- cQSAR
- clogP
- ClogP/CMR
- MOLEdb
- ChemDB/Datasets
- OCHEM
- E-Dragon
- PatternMatchCounter
- avogadro

Avogadro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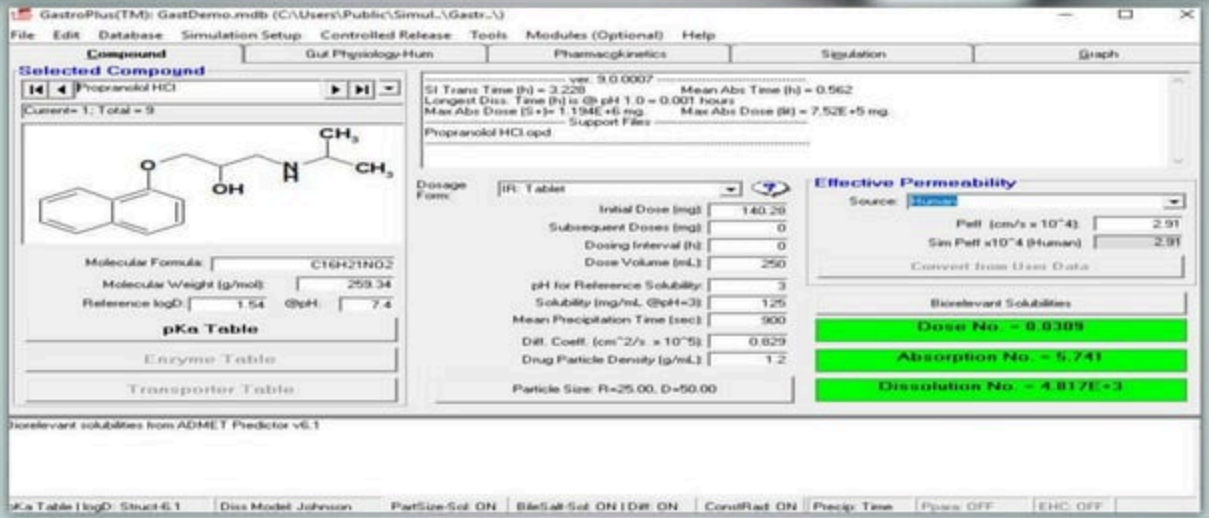
New Open Save Close Quit
Tool Settings...
Display Settings...
Navigate Settings
Display visual cues
View 1
Messages

ADME Toxicity

- VolSurf
- GastroPlus
- MedChemStudio
- ALOGPS
- OSIRISPropertyExplorer
- SwissADME
- Metrabase
- PACT-F, TOXNET

GastroPlus


GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul...\Gastr...\)
File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help
Compound
Gut Physiology-Hum
Pharmacokinetics
Simulation
Graph
Selected Compound
Propranolol HCl
Current= 1; Total = 9
Molecular Formula: C16H21NO2
Molecular Weight (g/mol): 259.34
Reference logD: 1.54 @pH 7.4
pKa Table
Enzyme Table
Transporter Table
ver. 9.0.0007
SI Trans Time (h) = 3.228 Mean Abs Time (h) = 0.562
Longest Diss. Time (h) is @ pH 1.0 = 0.001 hours
Max Abs Dose (S+)= 1.194E+6 mg. Max Abs Dose (R) = 7.52E+5 mg.
Support Files
Propranolol HCl.opd
Dosage Form: IR: Tablet
Initial Dose (mg): 140.29
Subsequent Doses (mg): 0
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Solubility (mg/mL @pH=3): 125
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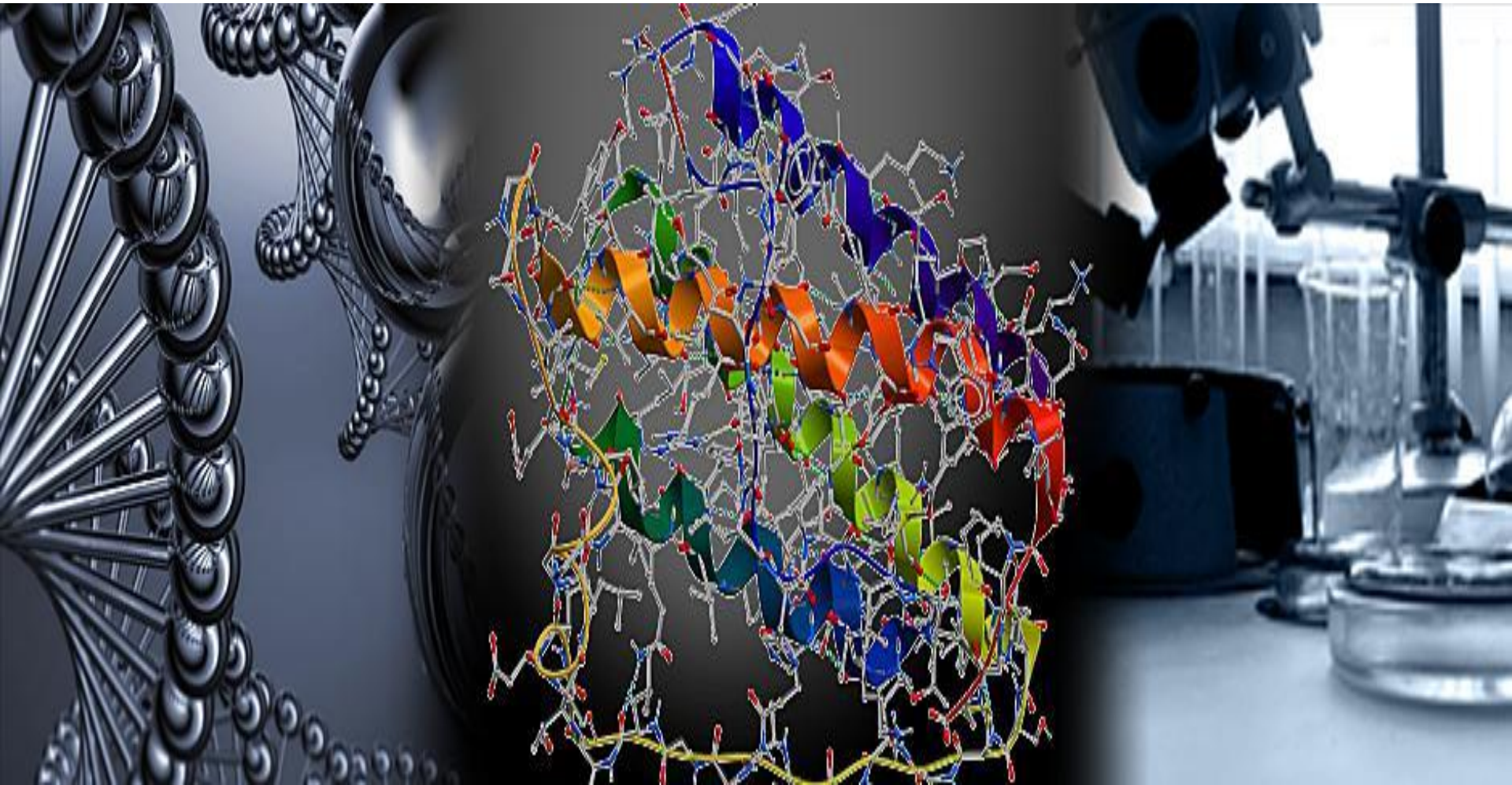
Drug Particle Density (g/mL): 1.2
Particle Size: R=25.00, D=50.00
Effective Permeability
Source: Human
Peff (cm/s x 10^4): 2.91
Sim Peff x10^4 (Human): 2.91
Convert from User Data
Biorelevant Solubilities
Dose No. = 0.8389
Absorption No. = 5.741
Dissolution No. = 4.817E+3
Biorelevant solubilities from ADMET Predictor v6.1
pKa Table | logD: Struct-6.1
Diss Model: Johnson
PartSize-Sol: ON
BileSalt-Sol: ON | Diff: ON
ConstRad: ON
Precip: Time
Ppara: OFF
EHC: OFF

That’s all. Thank you very much! ☺

Any Questions?

INTRODUCTION TO COMPUTER AIDED DRUG DESIGN



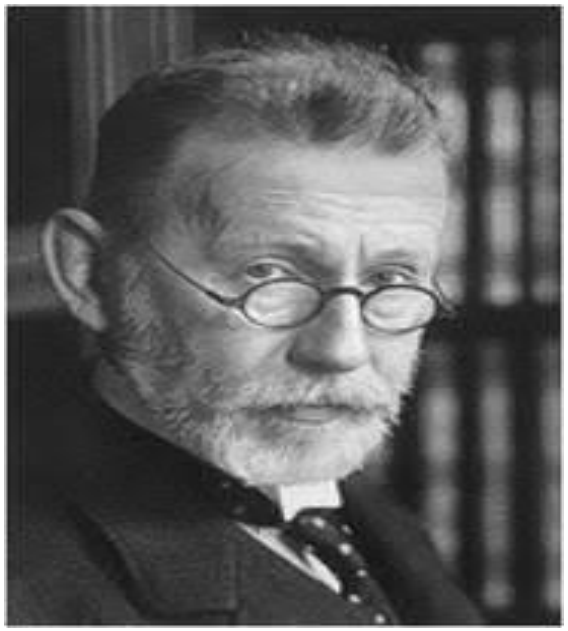
CONTENTS

- History.
- Different techniques.
- Applications.

HISTORY

1880-1930	Pharmaceutical industry started,established research laboratories to develop new drugs.
End of 19th century	Pharmacophore concept introduced by Paul Ehrlich
1900	Concept of lock and key-by Paul Ehrlich & E.Fischer.
1907	Arsphenamine synthesized-treatment of syphilis.
1960s	Attempt to relate chemical structure with biological action quantitatively.
Mid 1960	CADD was born as QSAR.
1970s	QSAR becomes most relevant in drug designing including 2D
1980s	1st computer based docking,data based combinatorial libraries.

1990s	Human genome project,Bioinformatics,Combinatorial chemistry,High-throughput screening.
1992	Methods for de-novo design.
2000s	Pharmacogenomics.

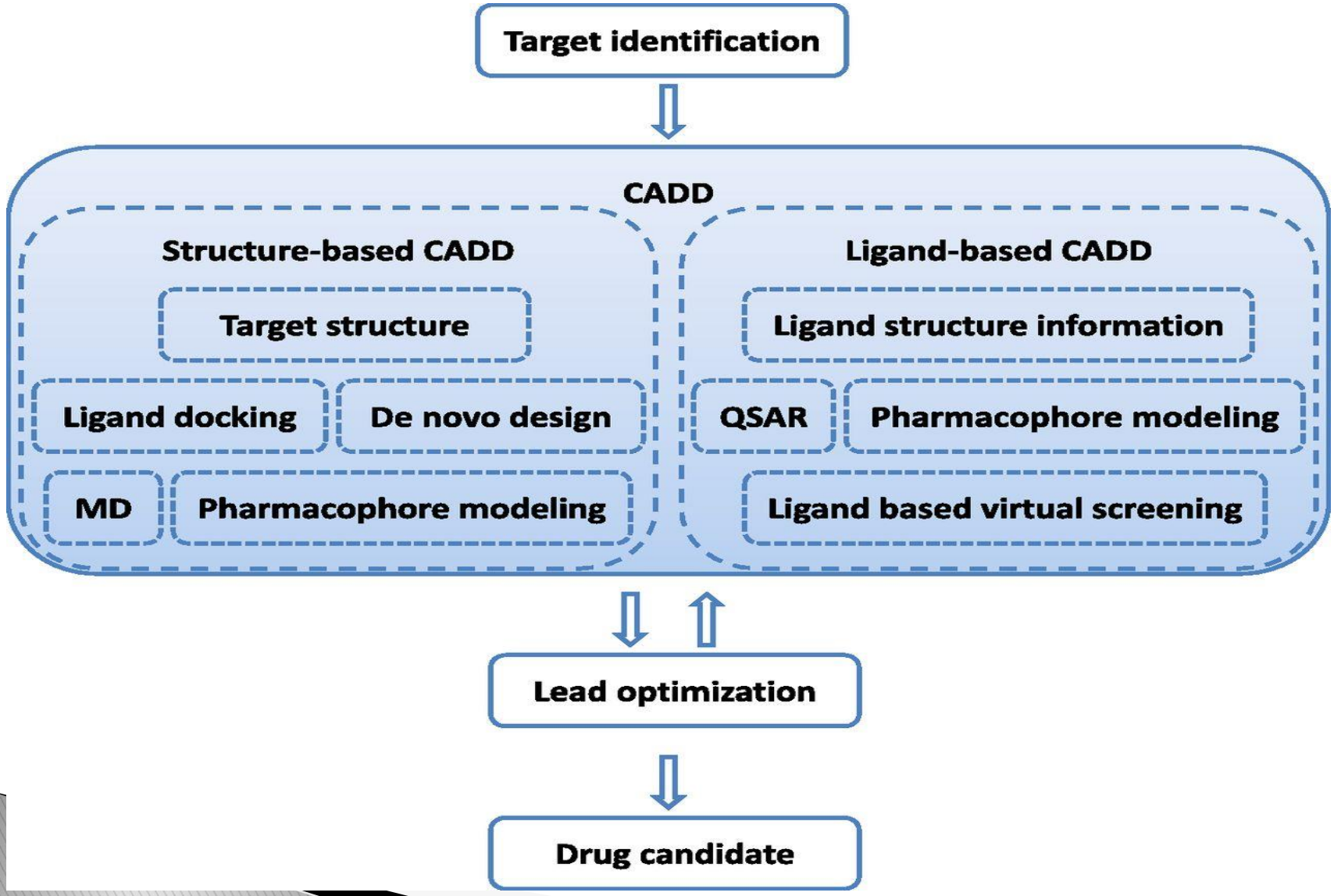


PAUL EHRLICH

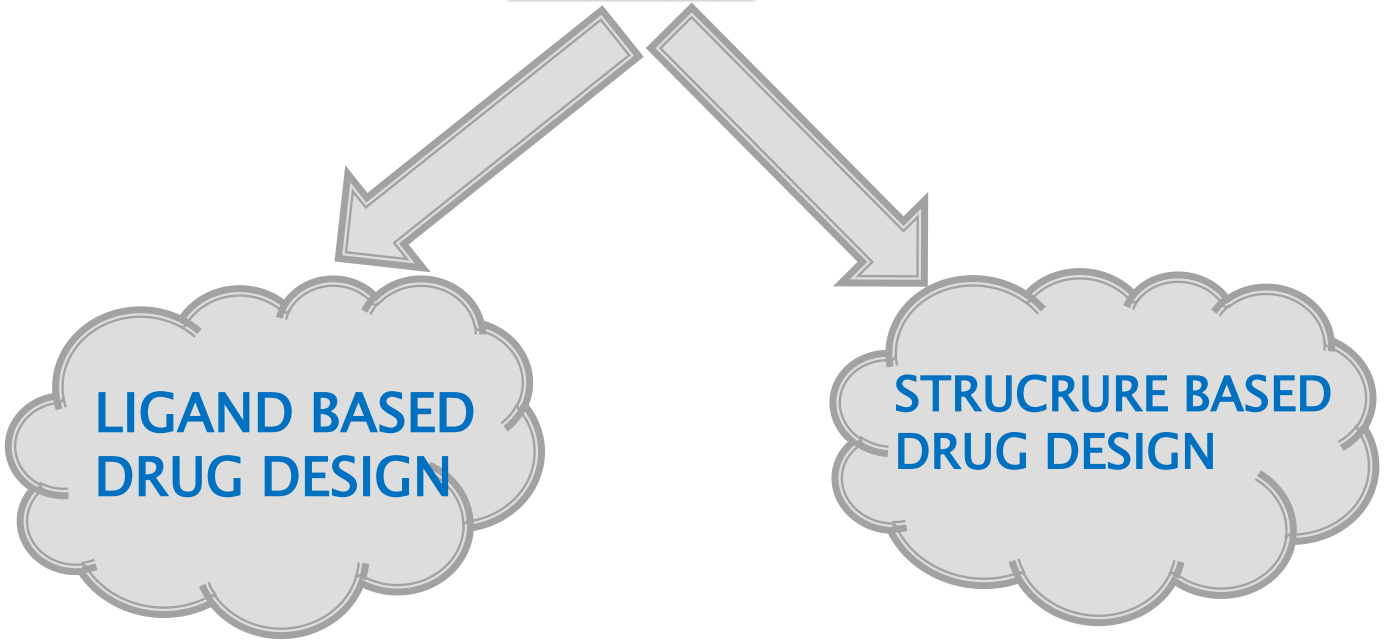
HERMAN EMIL FISCHER

- Numerous success designed drugs were reported,
- Dorzolamide- Cytoid macular edema
- Zanamavir- Influenza infection
- Sildenafil-Male erectile dysfunction
- Amprenavir-HIV

DIFFERENT TECHNIQUES IN CADD



TYPES



- LIGAND BASED DRUG DESIGN(LBDD)
- A model of biological target may be built on knowledge of what it binds to it,& this in turn used to design new molecules that interact with target.

STRUCTURE BASED DRUG DESIGN(SBDD)

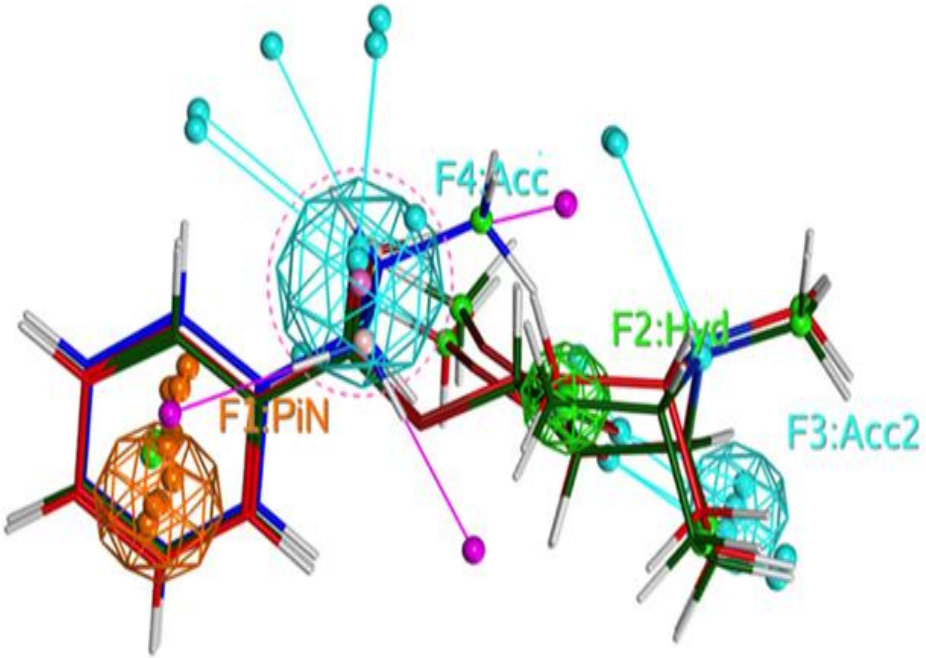
- 3D structure of biological target obtained through,

  X-ray crystallography

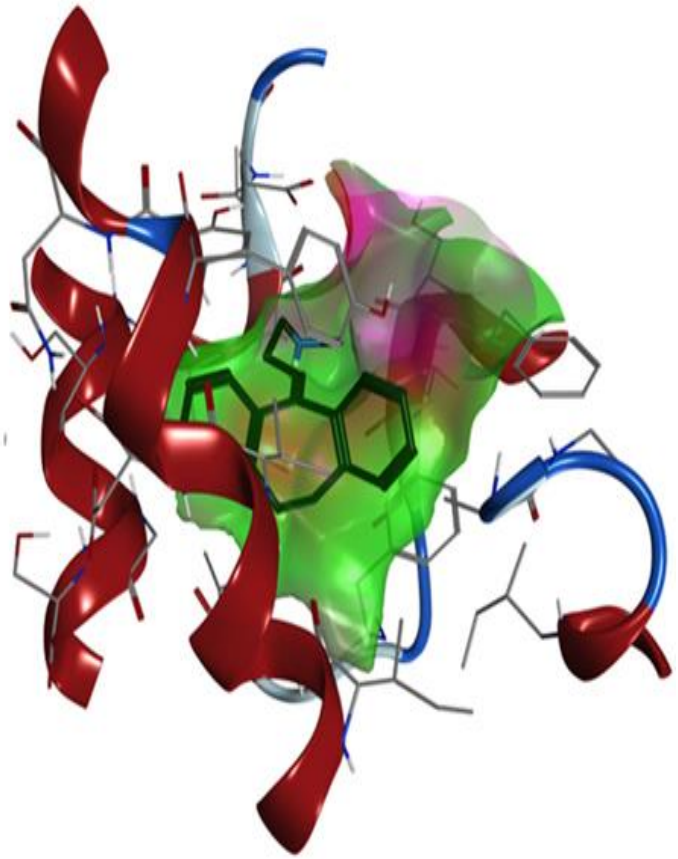
  NMR spectroscopy

- Using structure of biological target, candidate drugs are predicted to bind with high affinity & selectivity to the target are designed through computational procedures.

Ligand-Based Drug Design



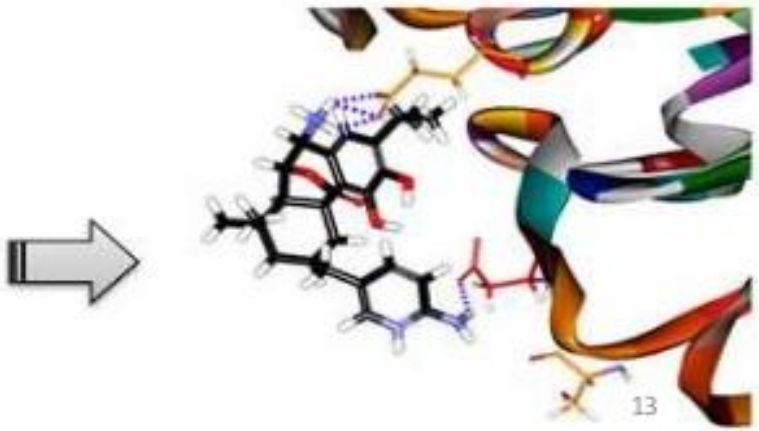
Structure-Based Drug Design



METHODS

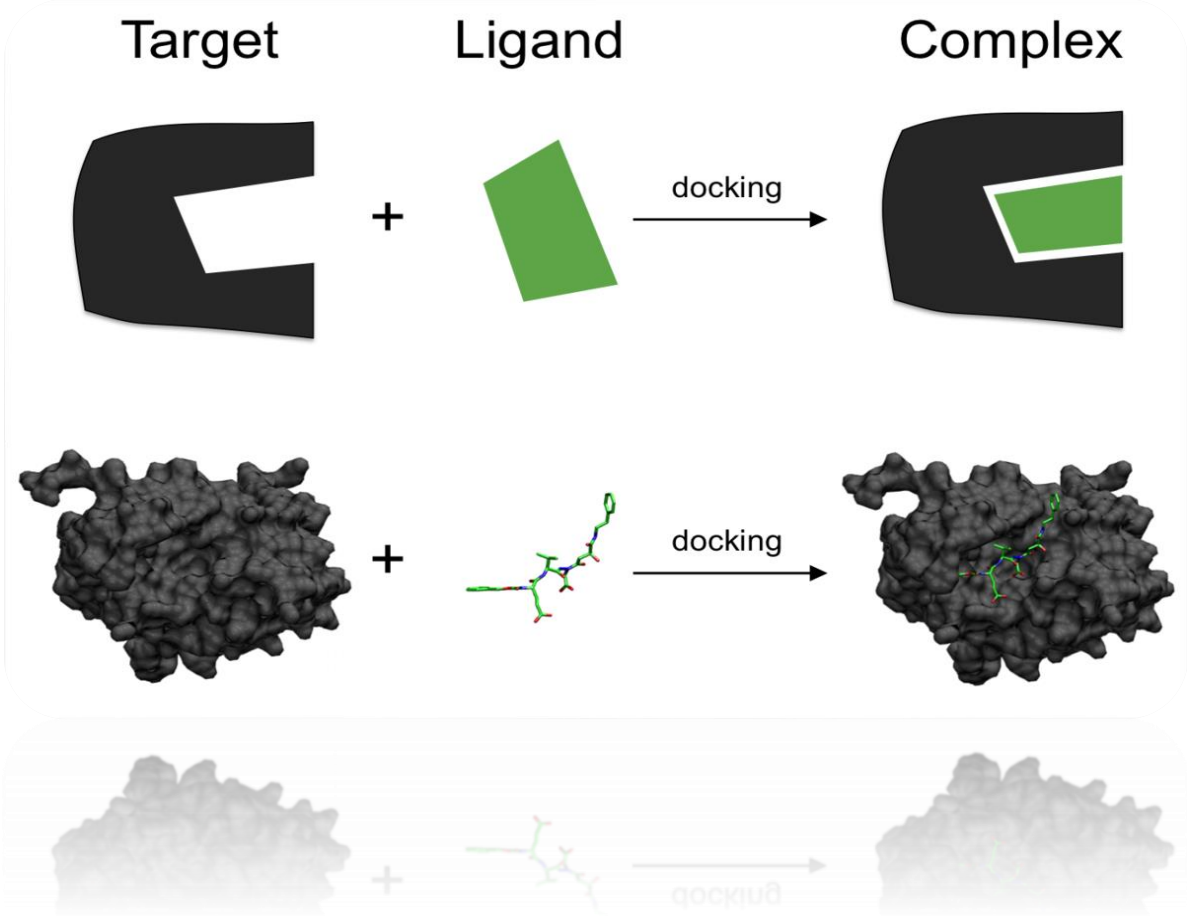
- VIRTUAL SCREENING
- Identification of new ligands for given receptor to find those fitting in binding pockets using docking programmes.
- DE-NOVO DESIGN
- Ligand molecules built up within the constraints of binding pocket by assembling small molecules.

large numbers of diverse structures

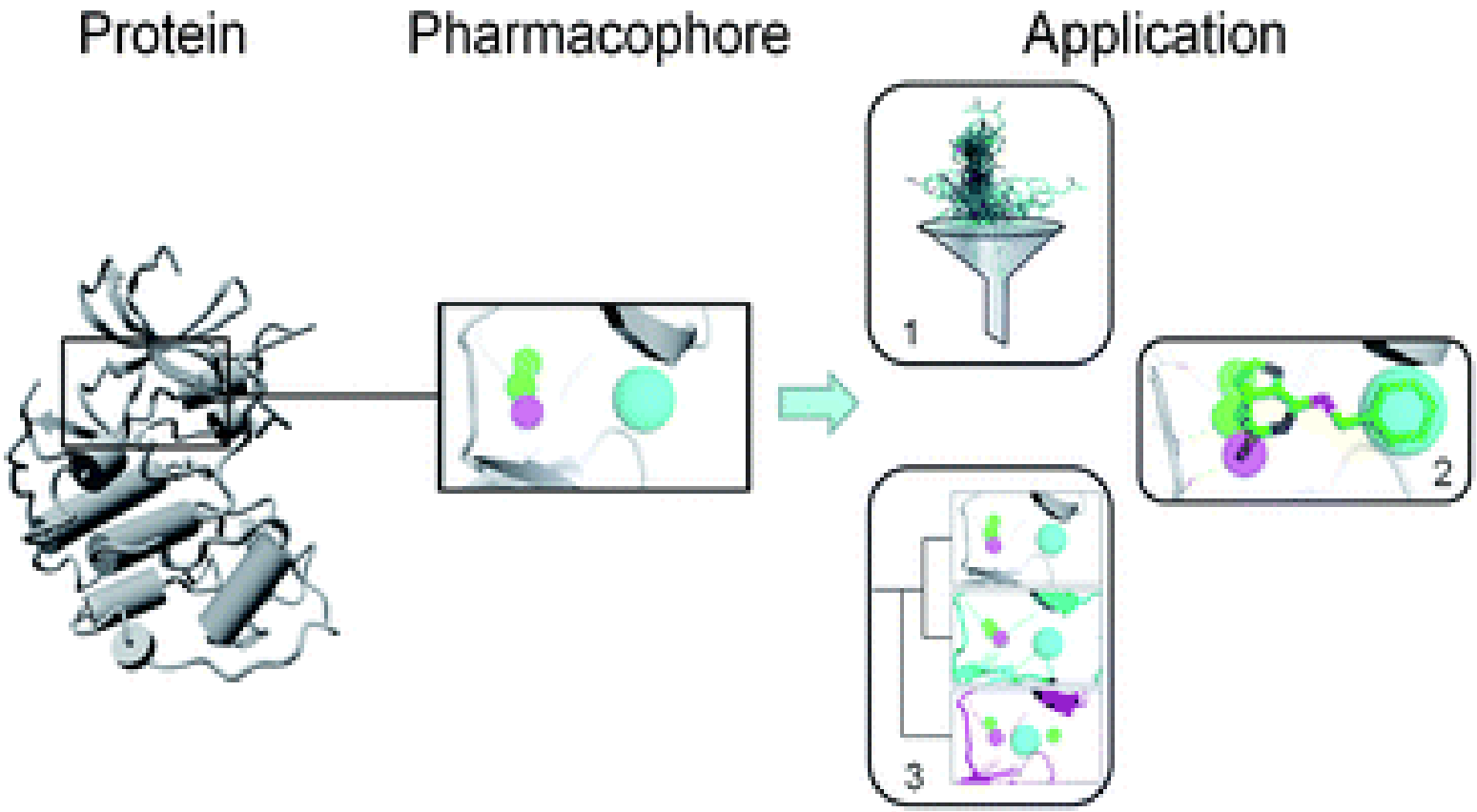


DOCKING

Attempts to find best matching between 2 molecules.

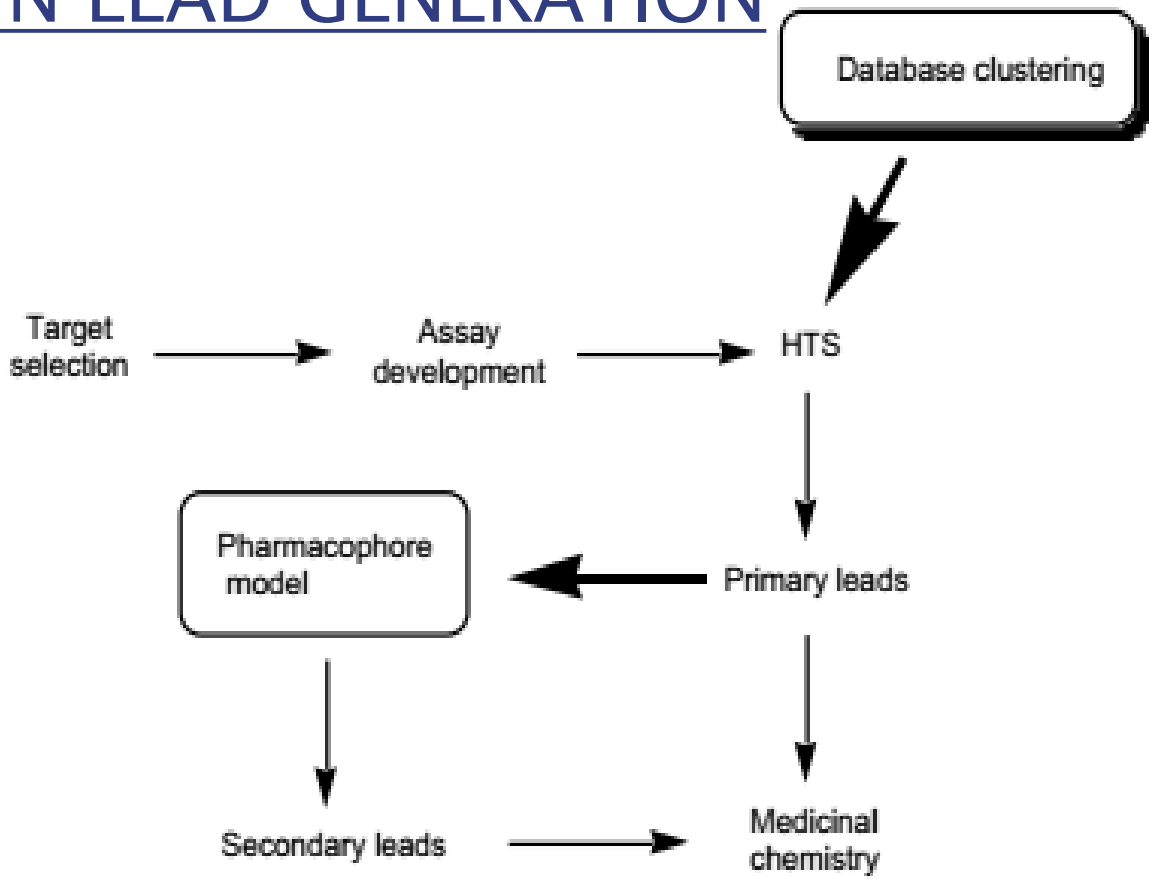


PHARMACOPHORE MODELLING



APPLICATIONS

CADD IN LEAD GENERATION



i. Summary of the use of CADD in focusing HTS process, designing secondary leads, and focusing medicinal chemistry

- CADD IN LEAD OPTIMIZATION
- Using QSAR methods that relate biological activities with stereoelectronic properties.
- MOLECULAR DOCKING
- To understand drug-receptor interaction
- FOLD RECOGNITION METHODS
- Model protein with sequence comparison method uses several databases.
- ADME/Tox properties
- Ionizability,lipophilicity,aqueous solubility etc

- E.g. of drugs designed through CADD
- Inhibitors of renin
- Inhibitors of dihydrofolate reductase
- Antiviral drug design
- Non-nucleoside reverse transcriptase inhibitors
- Opioid peptides
- Thrombin inhibitors

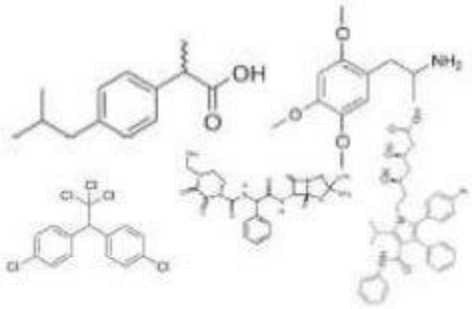
REFERENCES

- Gareth Thomas.Textbook of medicinal chemistry.Wiley Publishers:2007(2);112-124
- Pranta.P.kore,Madhavi.M.Mutha et.al. Computer aided drug design;an innovative tool for modelling.Open journal of medicinal chemistry,2012(2);139-148
- Application of computer aided drug design by Joo Chuan Tong
- Chun.Meng.Song et.al.Uses of computer aided drug design and discovery a review.International Journal of Pharmaceutical sciences.Vol 1 issue 2;2012

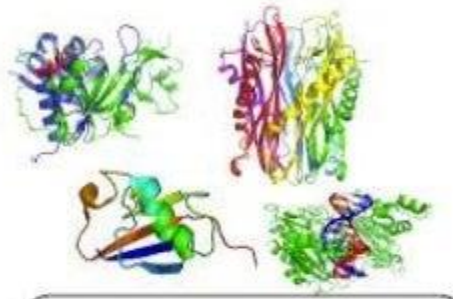
THANK YOU

MOLECULAR MODELING AND VIRTUAL SCREENING TECHNIQUES

Challenge in Drug Discovery



Chemical Space
$> 10^{20}$



Biological Space
10^4 to 10^5

Computational Screening, Experimental Screening

"Available" Compounds

Validated Targets

Choosing the right molecule

• **Goal:** to find a lead compound that can be optimized to give a drug candidate.

Optimization: using chemical synthesis to modify the lead molecule in order to improve its chances of being a successful drug.
• The challenge: chemical space is vast. Estimates vary

• There are ~65 million known compounds (example UniChem, PubChem)
• A typical pharmaceutical compound collection contains ~1-5 million compounds.

• High throughput screening allows large (up to 1 million) numbers of compounds to be tested
- But very small proportion of "available" compounds
- Large scale screening is expensive
- Not all targets are suitable for HTS

Virtual screening:

Virtual screening : a computational approach to assess the interaction of an *in silico* library of small molecules and the structure of a target macromolecule to rapidly identify new drug leads.

Merits:

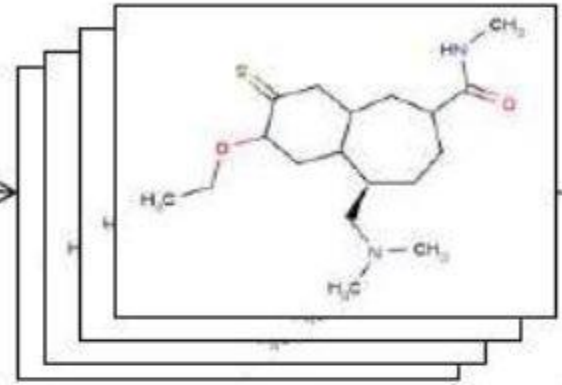
- **Computational**
- **Only high scoring ligands**
- **goes to assay**

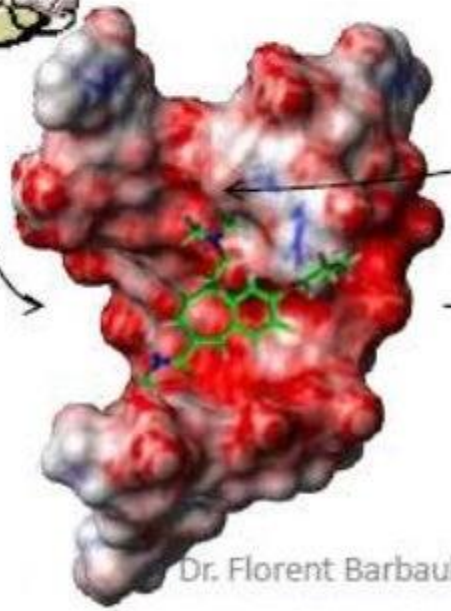
Demerits:

- **Molecular Complexity/ Diversity**
- **False Positives**
- **Synthesis Issue**

6.2. Virtual screening

6.2.1 Rules





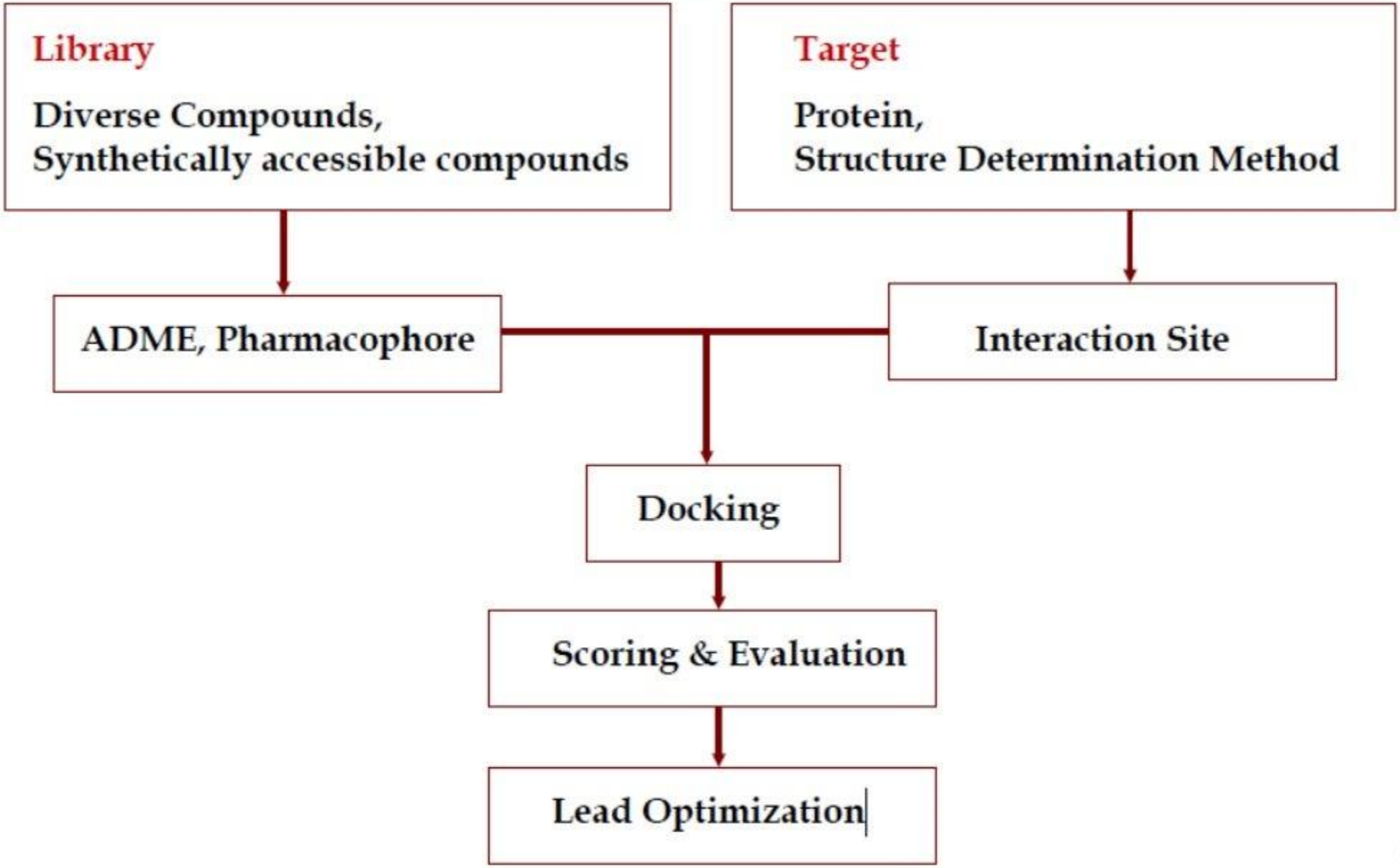
Ligand n°	ΔG
123	-12.3 kcal/mol
22	-11.7 kcal/mol
13	-10.1 kcal/mol
49	-9.3 kcal/mol
76	-6.5 kcal/mol

Dr. Florent Barbault, ITODYS (CNRS UMR 7086)

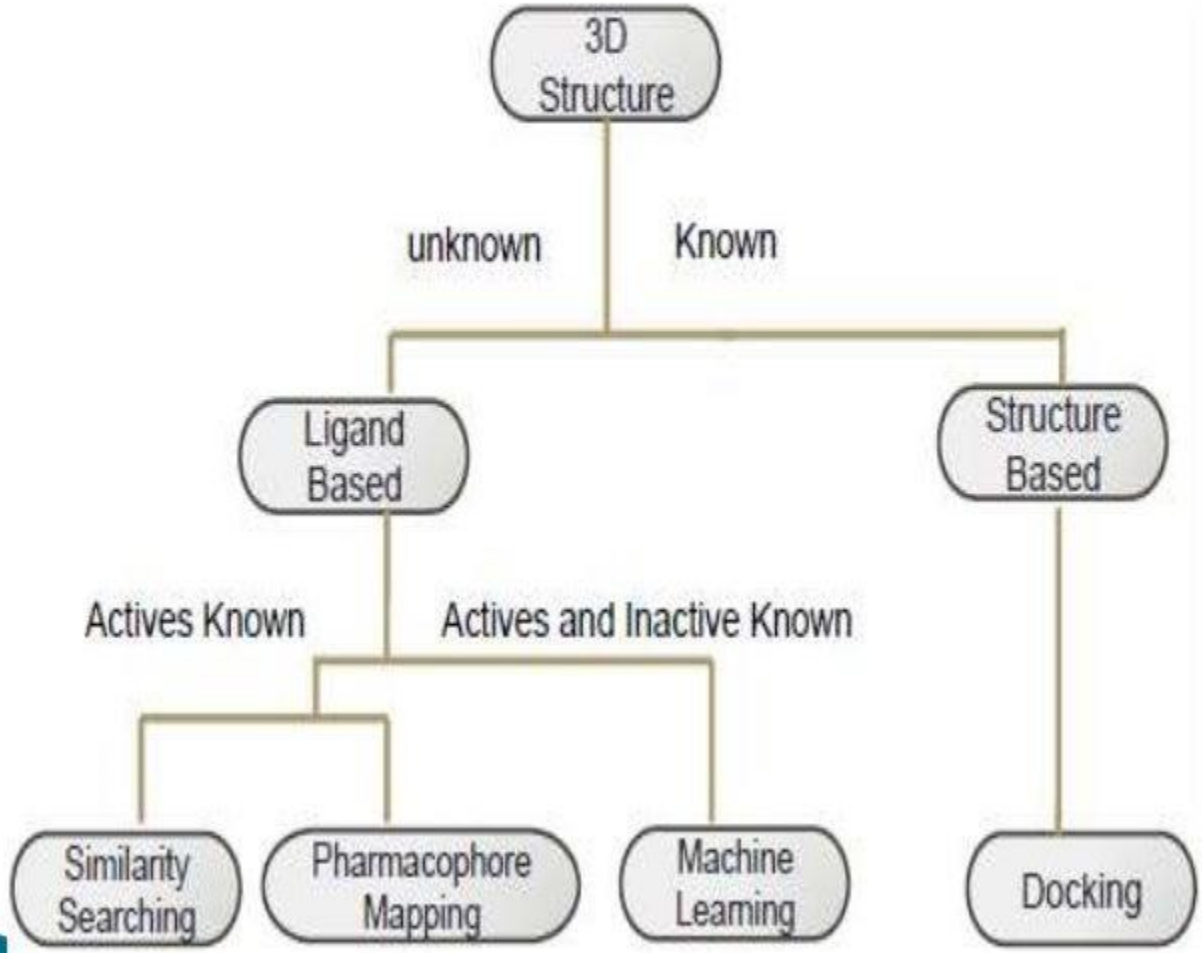
Virtual screening:

Advantage: compare to laboratory experiments are

- Low cost.
- Investigate compounds that not been synthesized yet.
- Virtual screening can be used to reduce the initial number of compounds be for using expensive HTS method.
- The number of passible virtual molecule available for virtual screening is much higher than there available for HTS


Library
Diverse Compounds,
Synthetically accessible compounds
Target
Protein,
Structure Determination Method
ADME, Pharmacophore
Interaction Site
Docking
Scoring & Evaluation
Lead Optimization

Virtual Screening



Depending upon structural and Bioactvity data available :

- *One or more actives molecule known perform similarity searching.*
- *Several active known try to identify a common 3D pharmacophore and then do 3D database search.*
- *Reasonable number of active and inactive known train a machine learning model.*
- *3D structure of protein known use protein ligand docking.*

ADME/T properties

Lipinski's RO5 and Ghose et al, 1999 profiling for druglikeness

MW < 500	better absorption and low level of allergic reactions
Hydrogen bond donors and acceptors < 5 and 10	circumvent non-specific binding
logP value < 5	low level of toxicity, non-specific binding and possible oral administration
logD pH (7.4) > 0	An indicator of lipophilicity of a drug; high level of metabolic clearance by P450 enzymes of liver were expected
Topological polar surface area (TPSA) > 60 Å2 and < 140 Å2	a high possibility of complete absorption

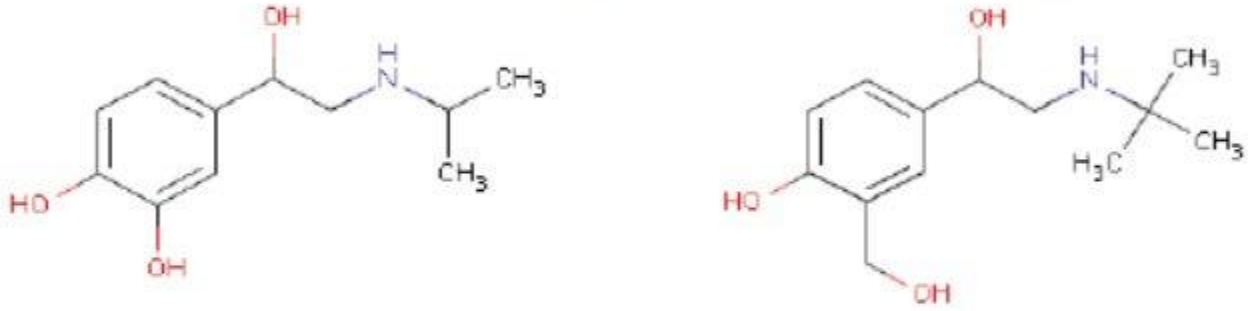
Similarity Searching

What is it ??

Chemical, pharmacological or biological properties of two compounds match.

The more the common features, the higher the similarity between two molecules.

Chemical



The two structures on top are chemically similar to each other. This is reflected in their common sub-graph, or scaffold: they share 14 atoms

Pharmacophore

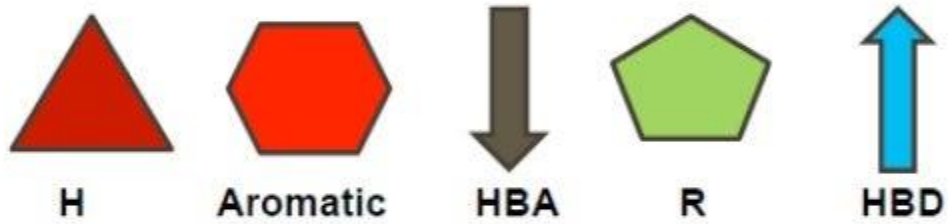
The two structures above are less similar chemically (topologically) yet have the same pharmacological activity, namely they both are Angiotensin-Converting Enzyme (ACE) inhibitors

What is required for a similarity search ?

- A Database SQL or NoSQL (Postgres, MySQL,MongoDB) or flat file of descriptors eg: ChemFP
- Chemical Cartridge to generate fingerprints(descriptors) for molecules (RDKit, openbabel)
- Similarity function to calculate similarity(Jaccard, Dice,Tversky) this can be written in c,c++ or python as a function inside SQL databases.

Pharmacophore searching

IUPAC Definition: "An ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".



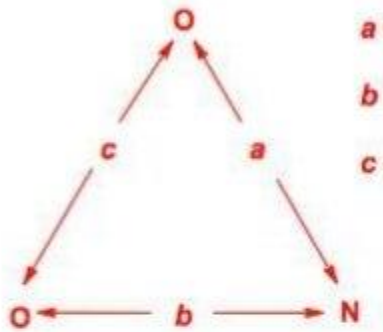
- In drug design, the term 'pharmacophore' refers to a set of features that is common to a series of active molecules.
- Hydrogen-bond donors and acceptors, positively and negatively charged groups, and hydrophobic regions are typical features.

We will refer to such features as 'pharmacophoric groups'.

3D- pharmacophores:

· A three-dimensional pharmacophore specifies the spatial relation-ships between the groups

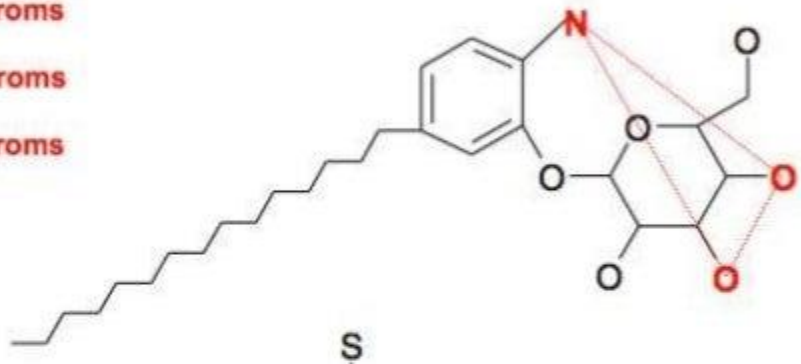
· Expressed as distance ranges, angles and planes

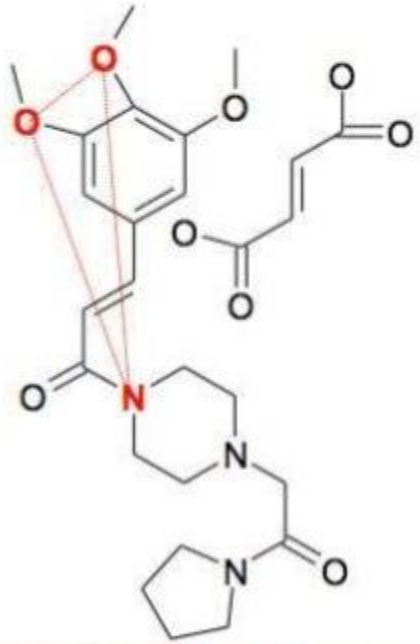


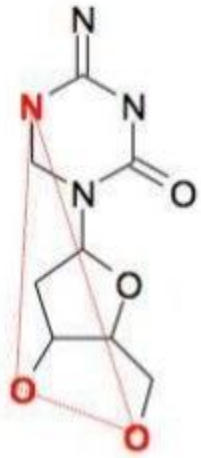
a = 8.62± 0.58 Angstroms

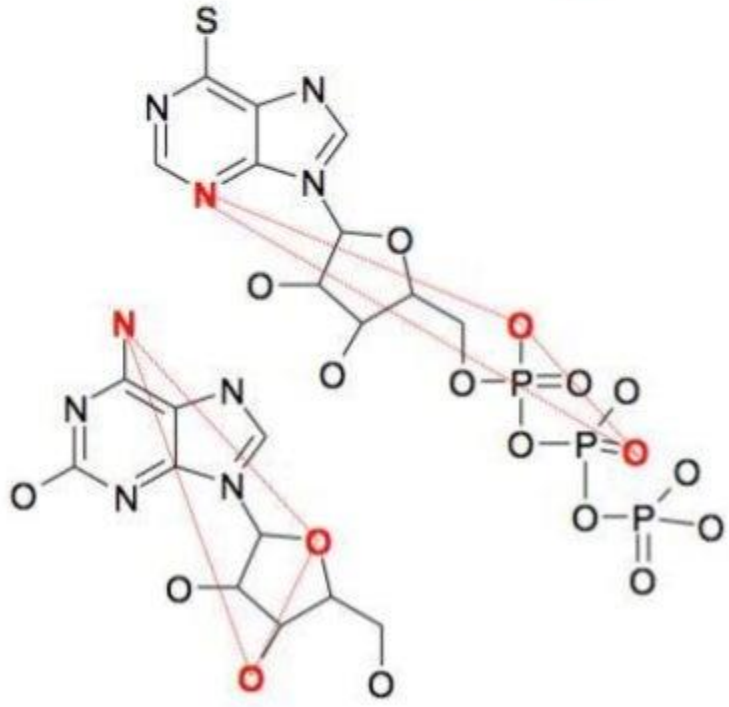
b = 7.08± 0.56 Angstroms

c = 3.35± 0.65 Angstroms

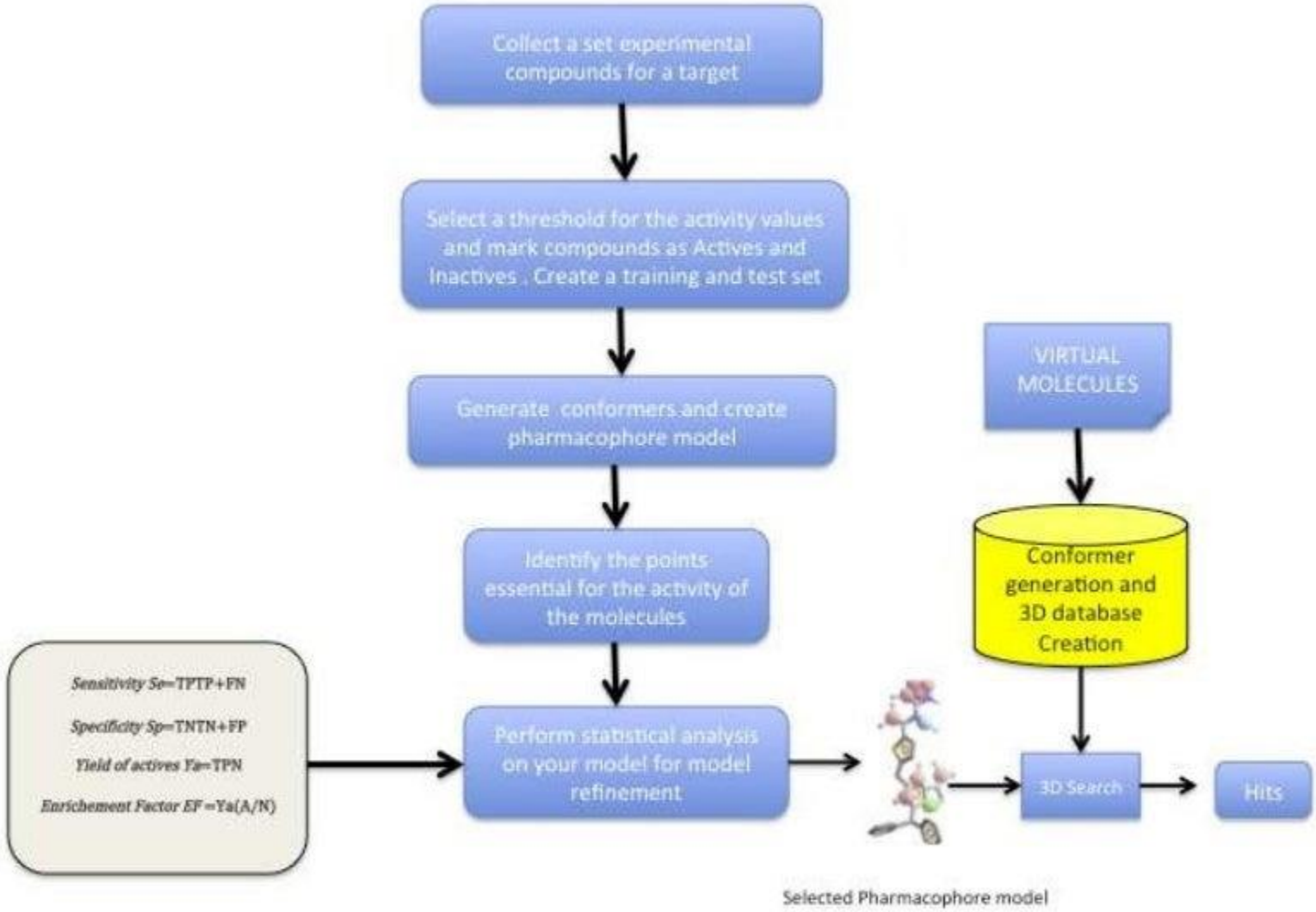








Workflow of pharmacophore modeling

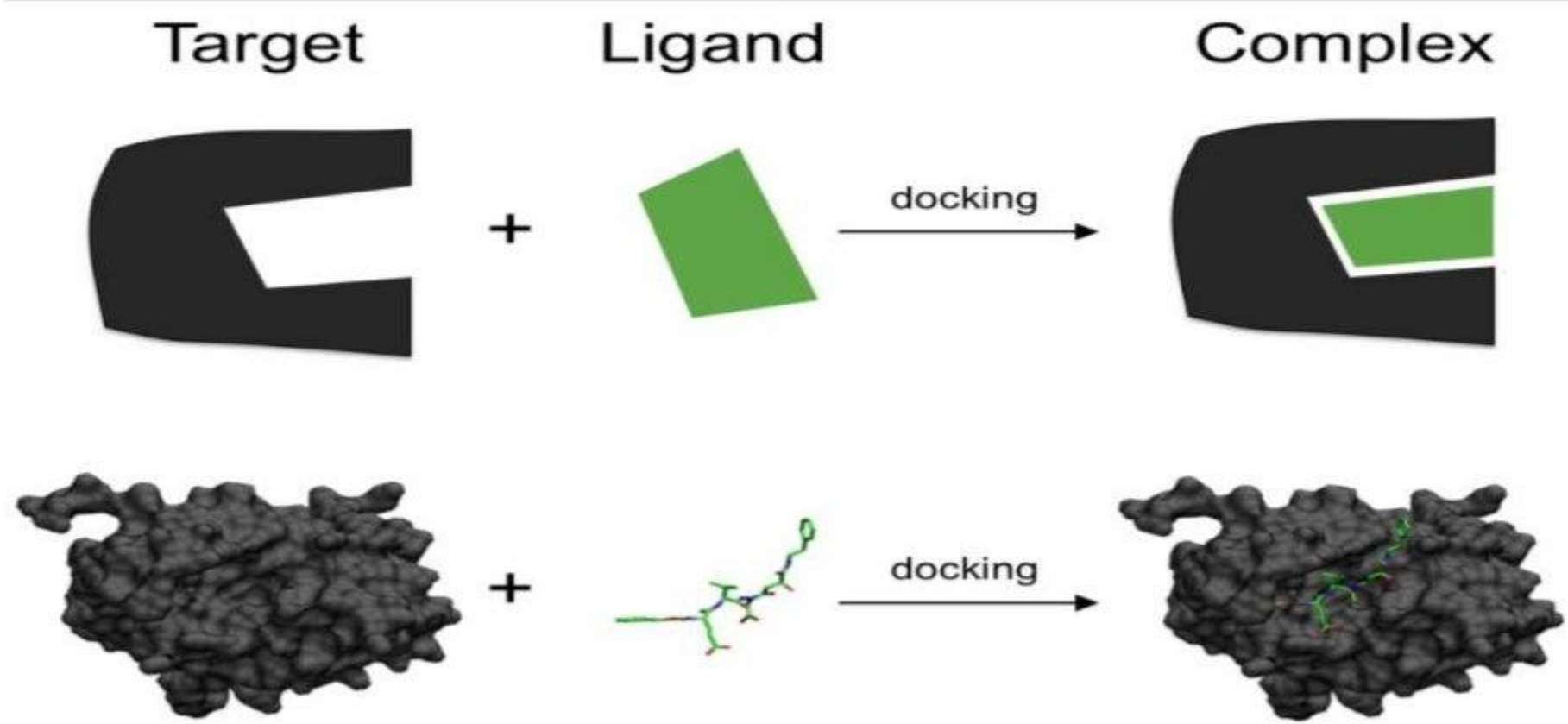


Tools to perform pharmacophore searching:

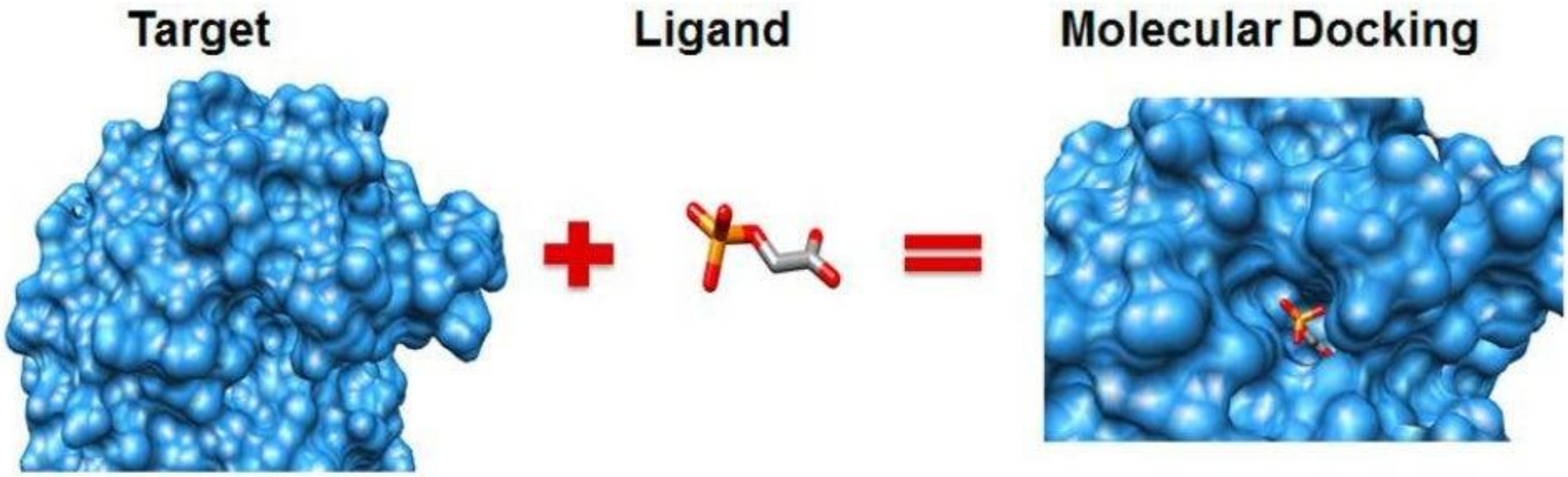
1) Catalyst (Accelrys)
2) Phase (Schrodinger)
3) LigandScout (Inte:Ligand)
4) PharmaGist
5) Pharmer
6) SHAFTS

Docking:

Computational simulation of a candidate ligand binding to a receptor.



Protein Ligand Docking



Computational method which mimics the binding of a ligand to a protein.
It predicts ..

a) the **pose** of the molecule in the binding site

b) The **binding affinity** or **score** representing the strength of binding

Pose and Binding Site:

- **Binding Site (or "active site")**

- the part of the protein where the ligand binds .
- generally a cavity on the protein surface.
- can be identified by looking at the crystal structure of the protein bund with a known inhibitor.

- **Pose ("binding mode")**

- the geometry of the ligand in the binding site
- Geometry- location , orientation and conformation of the molecule.

Protein Ligand Docking

• How does a ligand (small molecule) bind into the active site of a protein?

• Docking algorithms are based on two key components

– search algorithm

• to generate "poses" (conformation, position and orientation) of the ligand within the active site

– scoring function

• to identify the most likely pose for an individual ligand

• to assign a priority order to a set of diverse ligands docked to the same protein – estimate binding affinity.

Dock Algorithms

- DOCK: first docking program by Kuntz et al. 1982
  - Based on shape complementarity and rigid ligands
- Current algorithms
  - Fragment-based methods: FlexX, DOCK (since version 4.0)
  - Monte Carlo/Simulated annealing: QXP(Flo), Autodock, Affinity & LigandFit (Accelrys)
  - Genetic algorithms: GOLD, AutoDock (since version 3.0)
  - Systematic search: FRED (OpenEye), Glide (Schrödinger)

Scoring & Evaluation

The scoring process evaluates and ranks each ligand pose in the target site Energetically Favorable

Gibb's Energy

H-Bond Formation

Other Scores

The GScore is a combination of different parameters.

GScore = 0.065 * van der Waal energy + 0.130 * Coulomb energy + Lipophilic term + Hydrogen-bonding term + Metal-binding term + Buried polar groups penalty + Freezing rotatable bonds penalty + Active site polar interactions.

Scoring & Evaluation

PHARMACOPHORE MAPPING

WHAT IS PHARMACOPHORE ?

- First introduced in 1990 by “Paul Herilich”.
- A **pharmacophore is an abstract** description of molecular features which are necessary for molecular recognition of a ligand by a biological macromolecule.

- A pharmacophore is a representation of generalized molecular features including;
  - 3D (hydrophobic groups, charged/ionizable groups, hydrogen bond donors/acceptors)
  - 2D (substructures)
  - 1D (physical or biological)
- properties that are considered to be responsible for a desired biological activity.

WHAT IS PHARMACOPHORE MAPPING ?

- **Pharmacophore Mapping is the** definition and placement of pharmacophoric features and the alignment techniques used to overlay 3D.

- Two somewhat distinct usages:
- That substructure of a molecule that is responsible for its pharmacological activity (c.f. chromophore)
- A set of geometrical constraints between specific functional groups that enable the molecule to have biological activity

- The process of deriving pharmacophore is known as pharmacophore mapping.

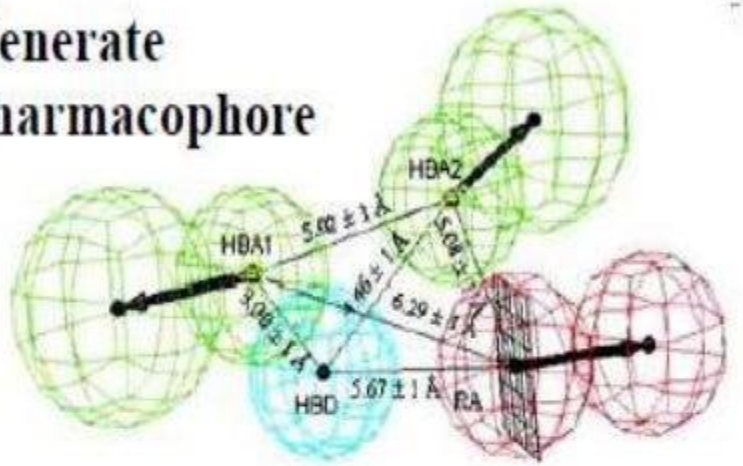
WHAT IS PHARMACOPHORE MAPPING ?

- It consist of three steps
- (1) identifying common binding element that are responsible for the biological activity;
- (2) generating potential conformations that active compound may adopt; and
- (3) determining the 3D relationship between pharmacophore element in each conformation generated.

Overview of Pharmacophore-based Drug Design

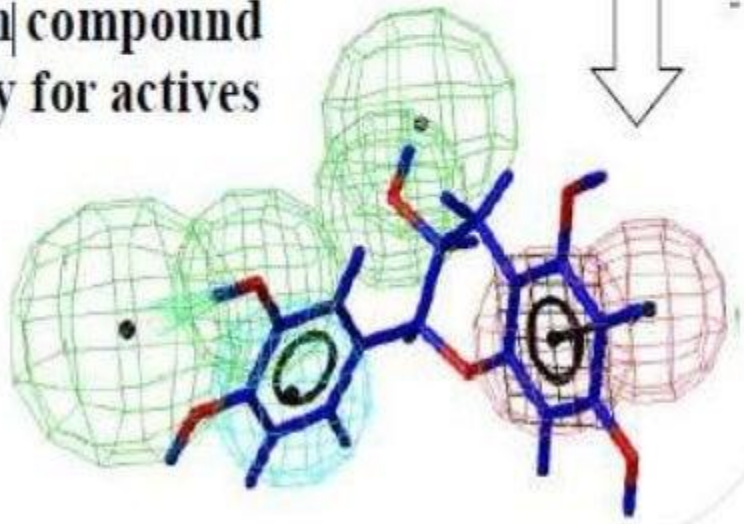
Activity data

Generate pharmacophore



Test activity

Search compound library for actives



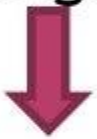
Buy or synthesise 'hits'

DRUG DESIGN

- The process of finding drug by design.

Based on what the drug targeting?

Metabolic or Signaling pathway



Specific for disease or pathology.

Drugs

Bind to active site & Work.

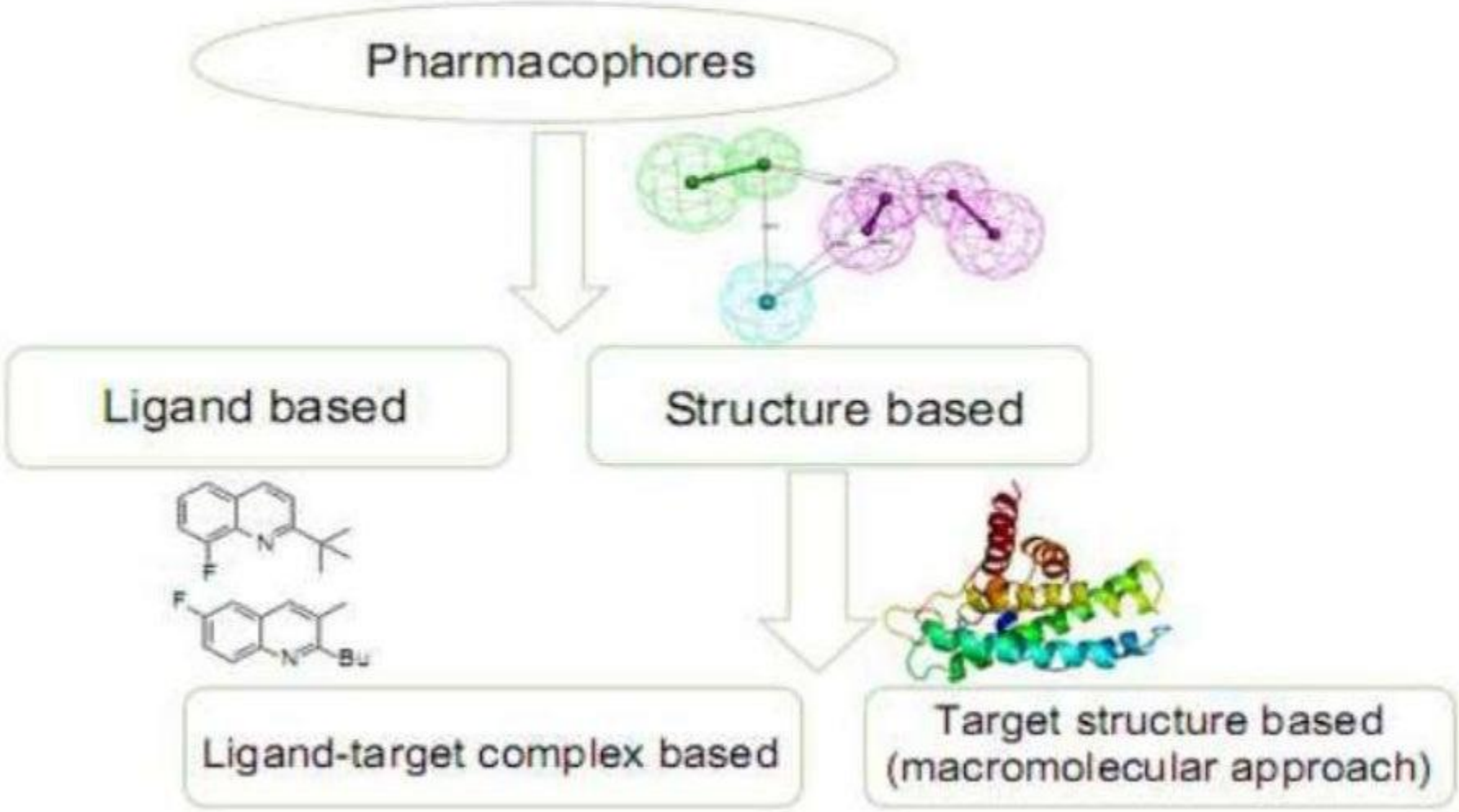
PHARMACOPHORE BASED SCREENING

- Usually pharmacophore based search are done in two steps.
- First the software checks whether the compound has the atom types or functional groups required by the pharmacophore,
- than its checks whether the spatial arrangement of this element matches the query.
- Flexible 3D searches identified a higher number of hits than rigid searches do.
- However flexible searches are more time consuming than rigid ones.
- There are two main approaches for including conformational flexibility in to the search
- one is top generate a user defined number of representative conformation for each molecules when the database is to created,
- the other is to generate conformation during the search.

PHARMACOPHORE BASED SCREENING

- Pharmacophore model provide powerful filter tools for virtual screening even in case where the protein structure is not available, pharmacophore filter are much faster than docking approaches, and there for greatly reduce the number of compound subjected to the more expensive docking application.
- Another interesting aspect of pharmacophore in virtual screening is 3D- pharmacophore diversity.

CLASSIFICATION



Classification of pharmacophore development methods.

PHARMACOPHORE BASED SCREENING

2-D Pharmacophore searching

- Searching of 2D database is of great importance for accelerating the drug discovery different strategies are pursued to search a 2D database to identified the compound of the interest Substructure search identified larger molecules that contain user define query irrespective of the environment in which the query substructure occur.
- Biochemical data obtainable from these compounds can be used for generating structure-activity-relationship (SAR) even before synthetic plans are made for lead optimization.
- In contrast, superstructure search are used to find smaller molecules that are embedded in the query.
- One problem that can arise from substructure search is that the number of the compound identified can reach into the thousands.
- One solution o this problem is raking of the compound based on similarity between compound in the database and in the query.

PHARMACOPHORE BASED SCREENING

- Beyond structure similarity, activity similarity has also been subject of several studies.
- Similarity search can be combined with substructure for limiting the number of compound selected.
- Flexible searches are used to identify the compound that differs from the query structure in user-specified ways.

3-D Pharmacophore searching

1.Ligand based pharmacophore generation

- Ligand based pharmacophores are generally used when crystallographic;solution structure or molded structure of protein cannot be obtained.
- When a set of active compound is known and it is hypothesized that all the compounds bind in the similar way to the protein, then common group should interact with the same protein residue.

PHARMACOPHORE BASED SCREENING

- Thus, a pharmacophore capturing this compound feature should be able to identified from a database novel compounds that binds to the same site of the protein as the known compounds do.

2. Manual pharmacophore generation

- Manual pharmacophore generation is used when there is an easy way to identify the common feature in a set of active compounds and/or there is experimental evidence that same functional groups should be present in the ligand for good activity.
- An example is the development of a pharmacophore model for dopamine-transporter (DAT) inhibitor.
- Pharmacophores should also have some flexibility built in, thus justifying the use of distance ranges.

PHARMACOPHORE BASED SCREENING

3. Automatic pharmacophore generation

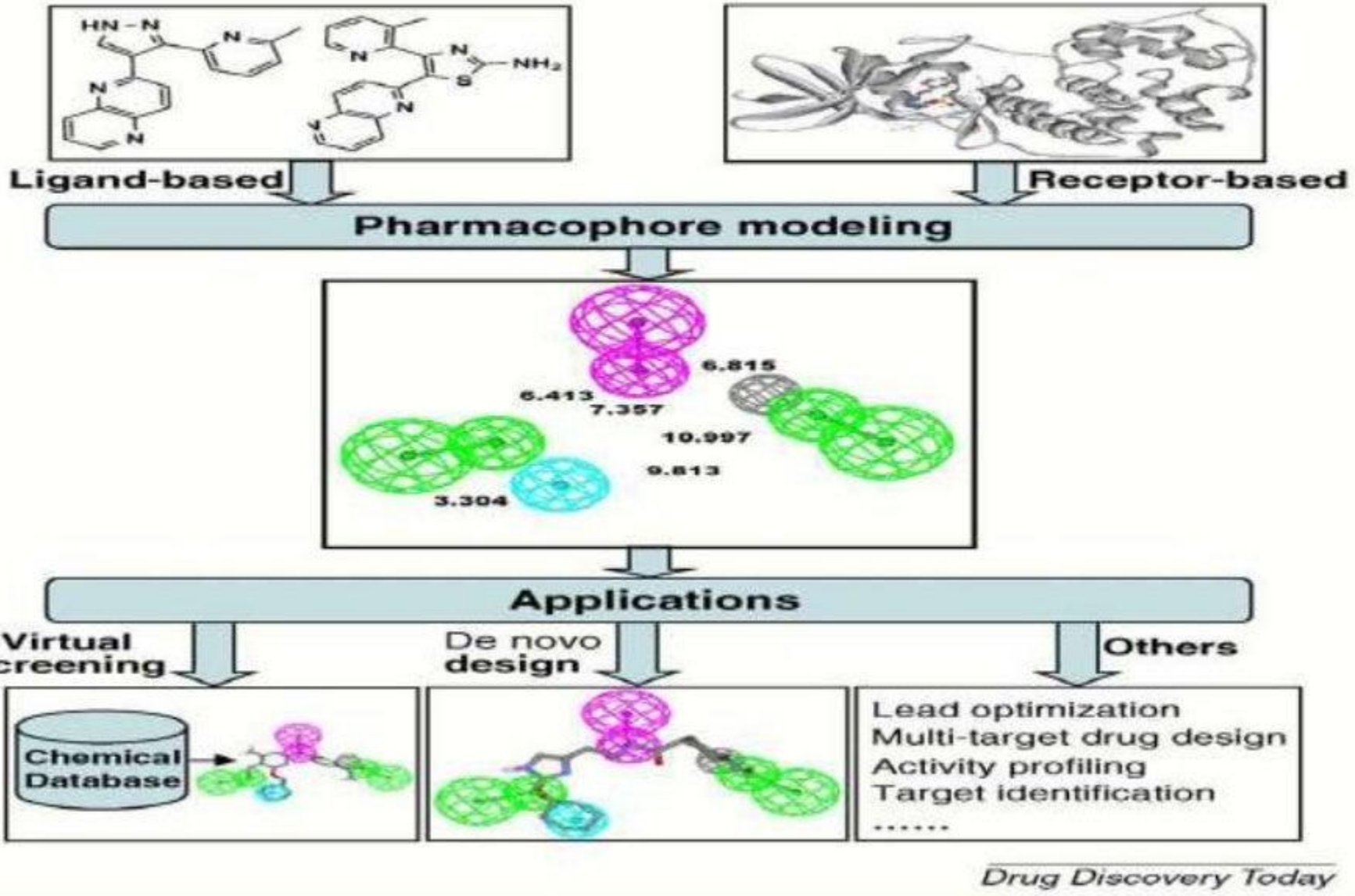
- Pharmacophore generation through conformational analysis and manual alignment is a very time consuming task, especially when the list of the active ligands is large and the elements of the pharmacophore model are not obvious.
- There are several programs Hip Hop, Hypogen, Disco, Gaps, flo, APEX, and ROCS, that can automatically generate potential pharmacophore from a list of known inhibitors.
- The performance of these programs in automated pharmacophore generation varies depending on the training set.
- These all program use algorithms that identified the common pharmacophore features in the training set molecules; they scoring function to rank the identified pharmacophores.

PHARMACOPHORE BASED SCREENING

4. Receptor based pharmacophore generation

- If the 3D structure of receptor is known, a pharmacophore model can be derived based on the receptor active site.
- Biochemical data used to identify the key residue that is important for substrate and/or inhibiting binding.
- This information can be used for binding pharmacophores targeting the region defined by key residue or for choosing among pharmacophore generated by automated program.
- This can greatly improve the chance of finding small molecules that inhibit the protein because the search is focused on a region of the binding side that is crucial for binding substrate and inhibitors.

APPLICATION



PHARMACOPHORE MAPPING SOFTWARE

- Discovery studio :
- Window ® and Linux® based protein modeling software.
- Produced by Accelrys software company.
- Easy to use interface.

- Examples of the programs that perform pharmacophore based searches are 3D search UNITY, MACCS-3D and ROCS.
- ROCS is using as shape based super position for identifying compound that have similar shaped.

References:

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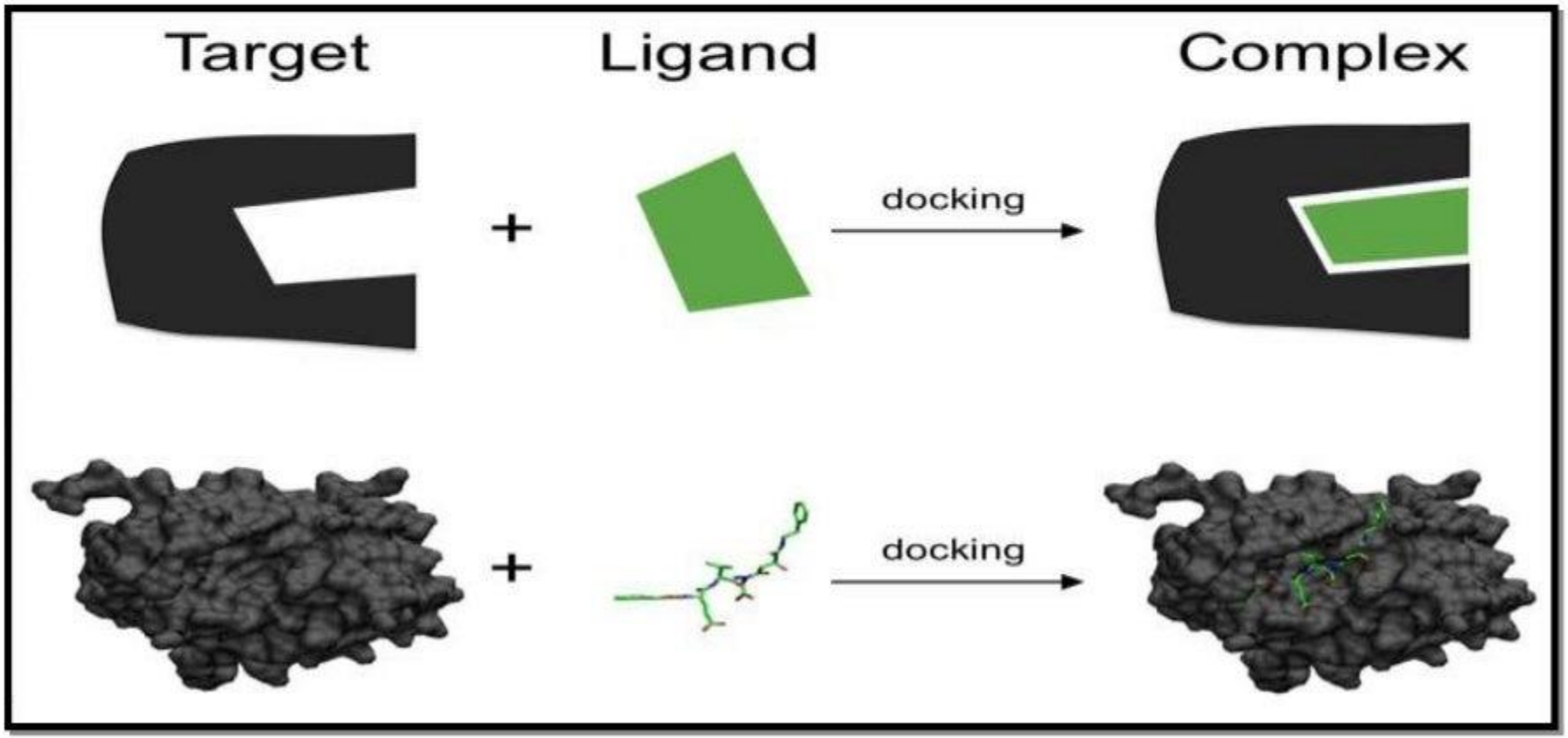
THANK YOU

TYPES AND SCREENING OF DOCKING

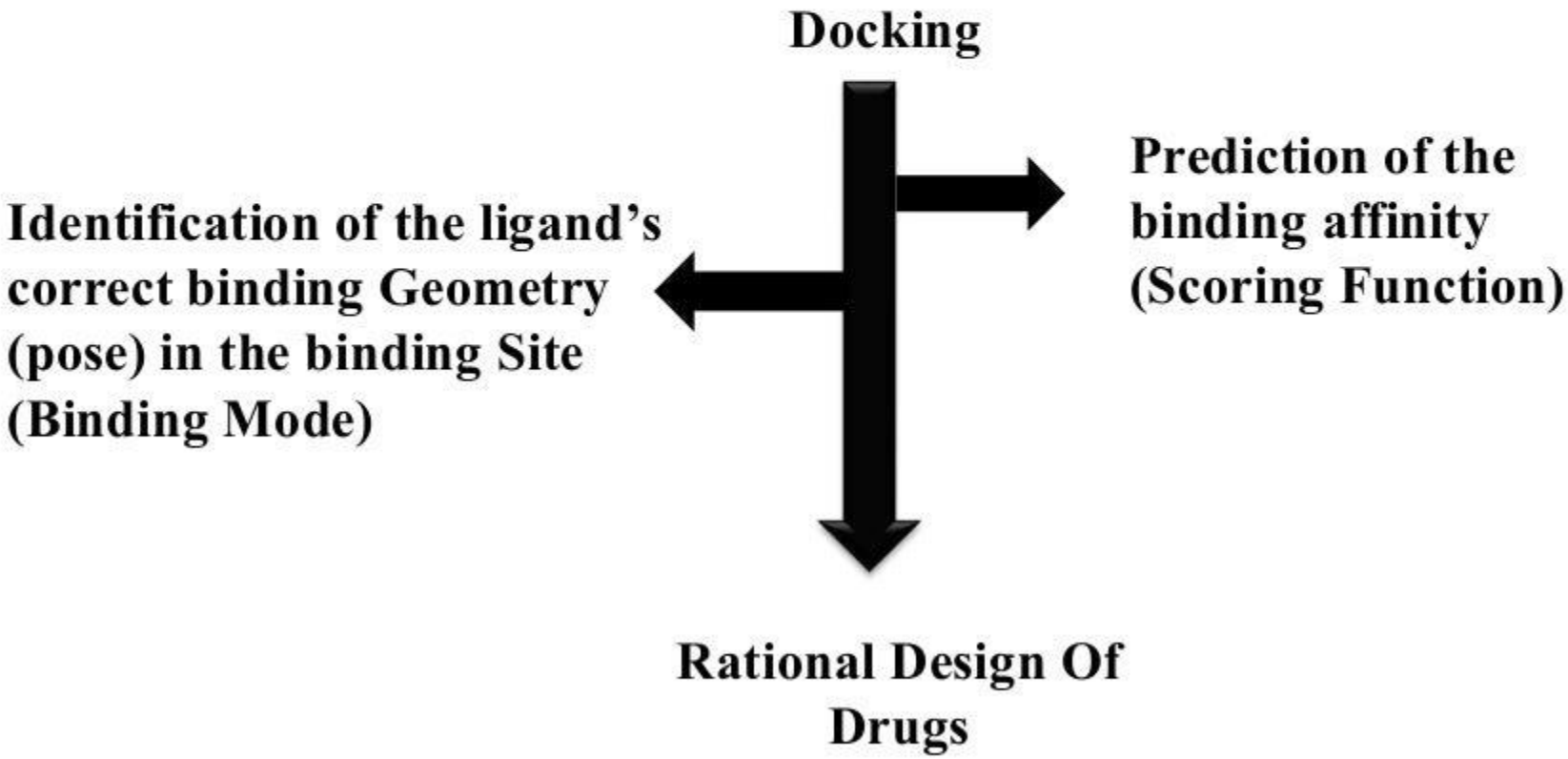
What Is Docking….?

- Docking attempts to find the "best" matching between two molecules
- Docking is a method which predicts the preferred orientation of one molecule to a second when bound to form a stable complex with overall minimum energy.



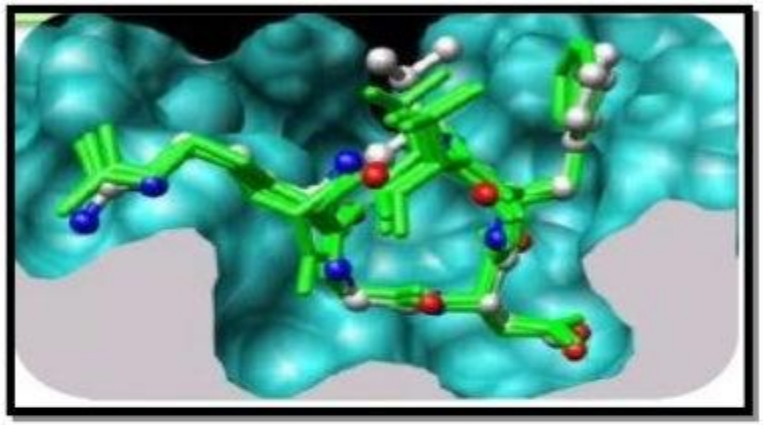
Why is docking important?

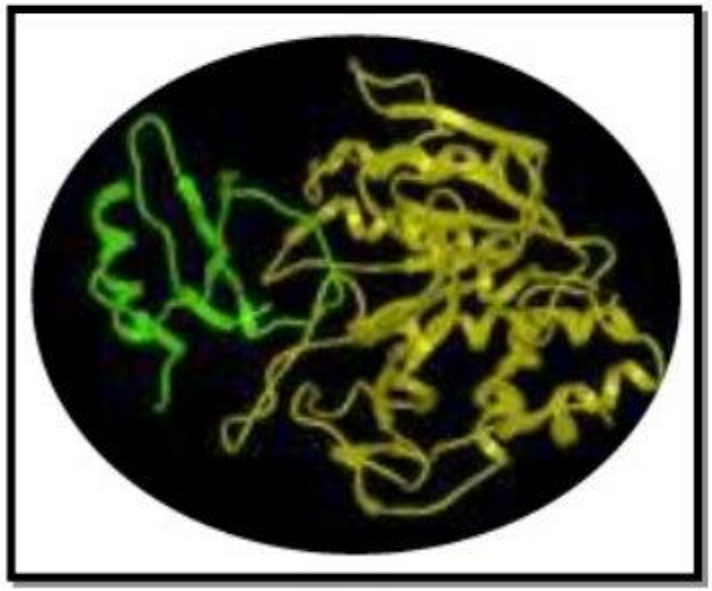
- It is of extreme relevance in **cellular biology**
- It is the key to rational **drug design**

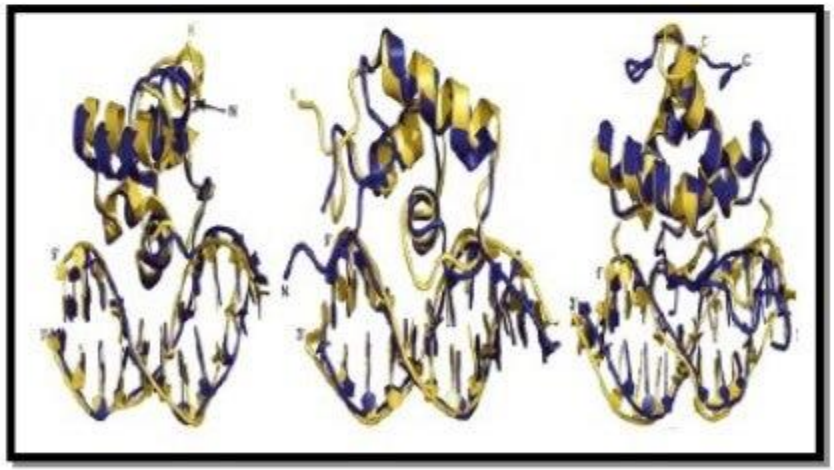


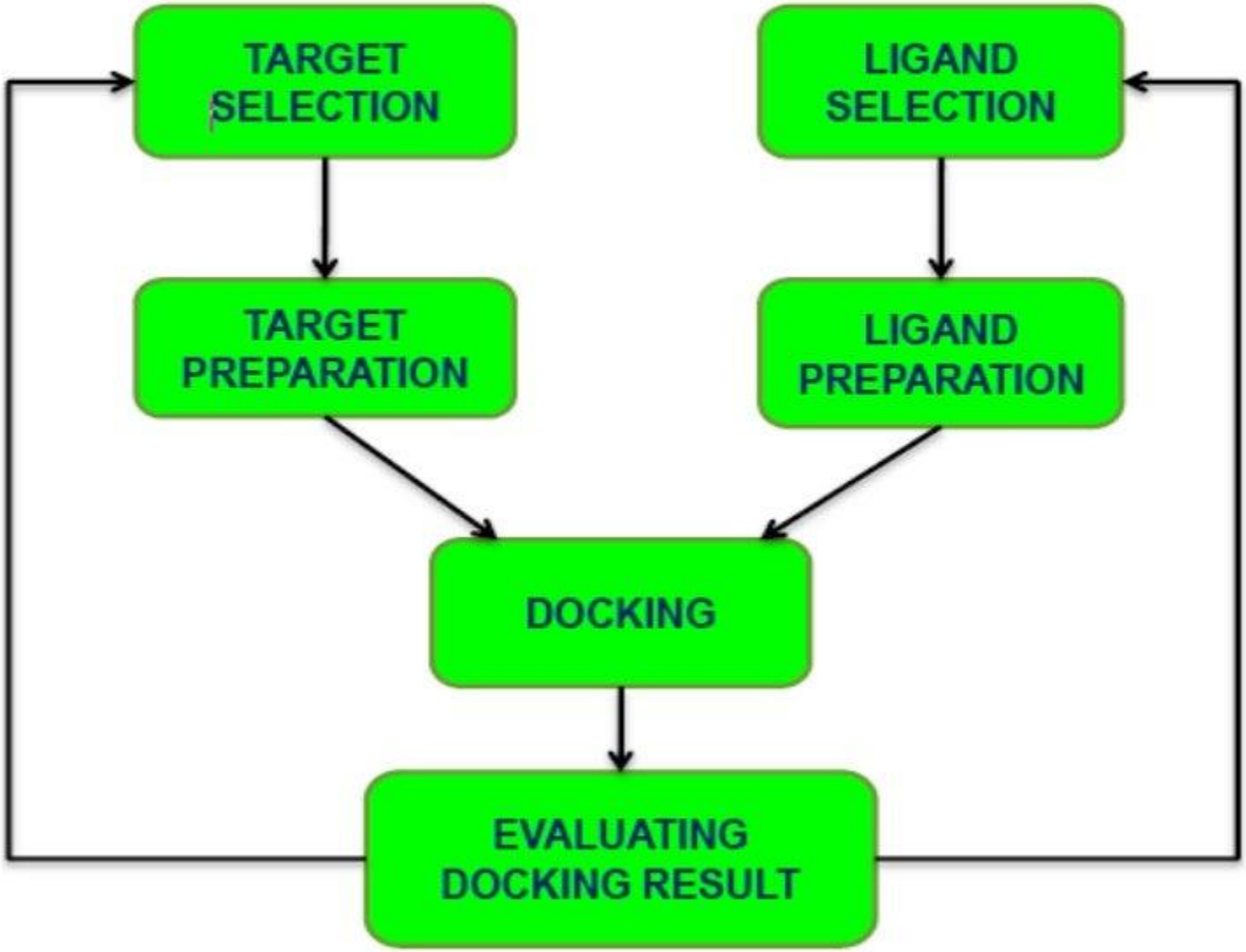
Docking can be between

- Protein - Ligand
- Protein – Protein
- Protein – Nucleotide



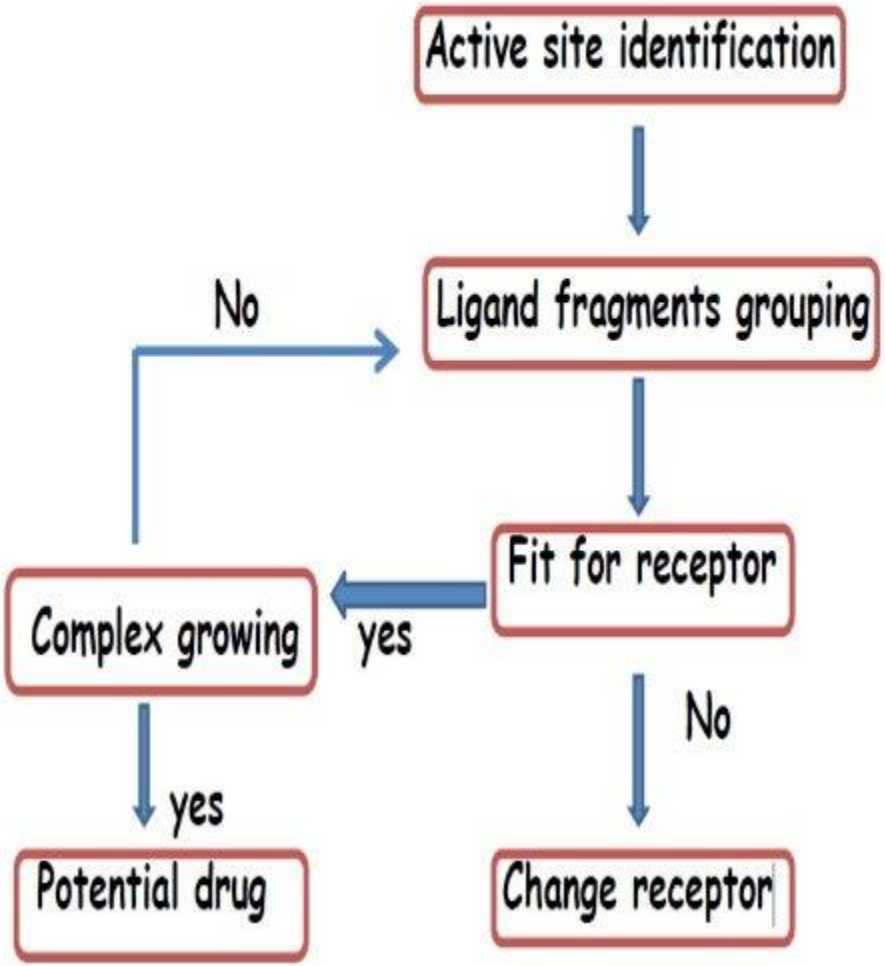




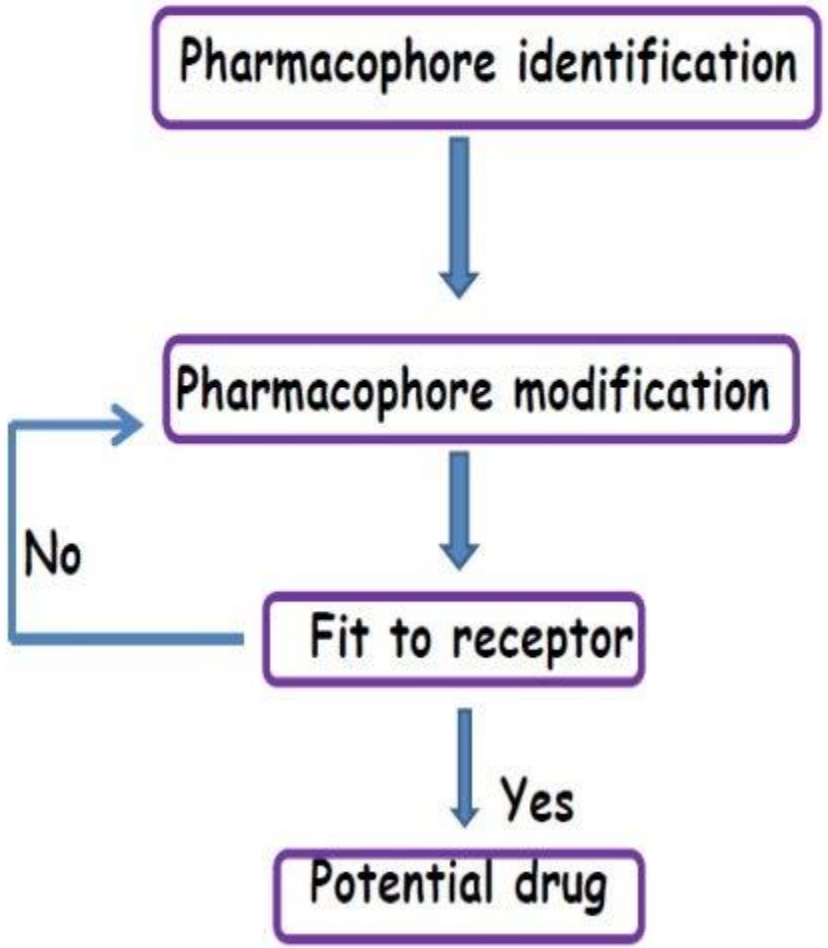

TARGET SELECTION
LIGAND SELECTION
TARGET PREPARATION
LIGAND PREPARATION
DOCKING
EVALUATING DOCKING RESULT

Key Stages In Docking

Receptor selection



Ligand selection



Types of docking

1. **Rigid Docking (Lock and Key)**

- In rigid docking, the internal geometry of both the receptor and ligand are treated as rigid.

2. **Flexible Docking (Induced fit)**

- An enumeration on the rotations of one of the molecules (usually smaller one) is performed. Every rotation the energy is calculated; later the most optimum pose is selected.

3. **Manual docking**

Manual docking

Dock or fit a molecule in the binding site

Binding group on the ligand and binding site are known, defined by the operator.

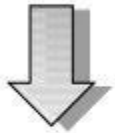
Binding group in the ligand is paired with its complementary group in the binding site

Ideal bonding distance for potential interaction is defined.

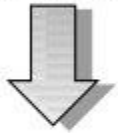
Docking procedure is started

The program try to get best fit, as defined by the operator

The paired groups are not directly overlaid, they are , fitted within preferred bonding distance

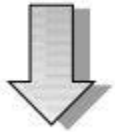


Both ligand and protein remain same conformation throughout the process



So this is a rigid fit, once a molecule successfully docked fit optimization is carried out.

Same as in energy minimization



Different conformation of molecule can be docked to in same way

Identify the best fit

Software's

- **SANJEEVINI** – IIT Delhi (www.scfbio-iitd.res.in/sanjeevini/sanjeevini.jsp)
- **GOLD** – University of Cambridge ,UK (www.ccdc.cam.ac.uk/Solutions/GoldSuite/Pages/GOLD.aspx)
- **AUTODOCK** - Scripps Research Institute,USA (autodock.scripps.edu/)
- **GemDock (Generic Evolutionary Method for Molecular Docking)** - A tool, developed by Jinn-Moon Yang, a professor of the Institute of Bioinformatics, National Chiao Tung University, Taiwan (gemdock.life.nctu.edu.tw/dock/)
- **Hex Protein Docking** - University of Aberdeen, UK (hex.loria.fr/)
- **GRAMM (Global Range Molecular Matching) Protein docking** - A Center for
- Bioinformatics, University of Kansas, USA (www.bioinformatics.ku.edu/files/vakser/gramm/)

Applications

- **Virtual screening (hit identification)** docking with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest.
- **Drug Discovery (lead optimization)** docking can be used to predict in where and in which relative orientation a ligand binds to a protein (binding mode or pose). This information may in turn be used to design more potent and selective analogs.
- **Bioremediation** Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes.

Docking based screening

1) Virtual based screening
2) Molecular based screening

Molecular based screening

- Docking- the process by which molecular modeling software fits a molecule into target binding sites.
- Used for finding binding modes of protein with ligands/inhibitors
- In molecular docking, attempt to predict the structure of the intermolecular complex formed between two or more molecules.

Molecular docking tries to predict the structure of the intermolecular complex formed between two or more constituent molecules.

Molecular docking has become an increasingly important tool for drug discovery.

Steps Involve in molecular docking

IN-silico generation of ligands(using chemsketch in this software we can draw the structure of Ligand/molecule).

Conversion of file format(OPEN BABEL is the software used to converting format of file .mol to .pdb

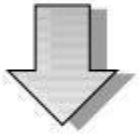
Protein optimization(RCSB- protein data bank, here you can prepare your protein of interest for docking).

Energy Minimization(here SPDV swiss-Pdb viewer software) This can be done by commanding.

Molecular docking (creation of .gpf-grid parameter file and .dpf-dock parameter file. Autodock Vina, Autodock 4.0, Autodock 4.2

This are the software used to make auto griding and dock parameters along with grid mapping.

Running the docking algorithm(CYGWIN-1 in this software we will create GLG file and DLG file here this software works commanding after getting succesfull comand for auto grid(glg) and auto dock (dlg)



After this step we got to know minimal binding energy CYGWIN-2

Hydrogen bond analysis(UCSF CHIMERA we use this software for visulisation and analysis of result.

ADMET(the molecules which have shown H bond with the active site residue or any other residue of the binding pocket note down those molecules and then run these molecule on the online ADMET serve.

Applications

1. Structure based drug design.
2. Lead Optimization.
3. Virtual Screening.
4. Protein-Protein Docking.
5. Chemical mechanism studies.

DE NOVO APPROACHES

- De novo design is the approach to build a customized Ligand for a given receptor.
- This approach involves the ligand optimization.
- Ligand optimization can be done by analyzing protein active site properties that could be probable area of contact by the ligand.
- The analyzed active site properties are described to negative image of protein such as hydrogen bond, hydrogen bond acceptor and hydrophobic contact region.

DE NOVO DRUG DESIGN

- De novo means **start afresh, from the beginning, from the scratch.**
- It is a process in which the 3D structure of receptor is used to design newer molecules.
- It involves structural determination of the lead target complexes and lead modifications using molecular modeling tools.
- Information available about target receptor but no existing leads that can interact.

Procedure

- Crystallise target protein with bound ligand
- (e.g. enzyme + inhibitor or ligand)
- Acquire structure by X-ray crystallography
- Identify binding site (region where ligand is bound)
- Remove ligand
- Identify potential binding regions in the binding site
- Design a lead compound to interact with the binding site
- Synthesise the lead compound and test it for activity
- Crystallise the lead compound with target protein and identify the actual binding interactions
- Structure based drug design

Types of De Novo Drug Design And Differences

Manual Design

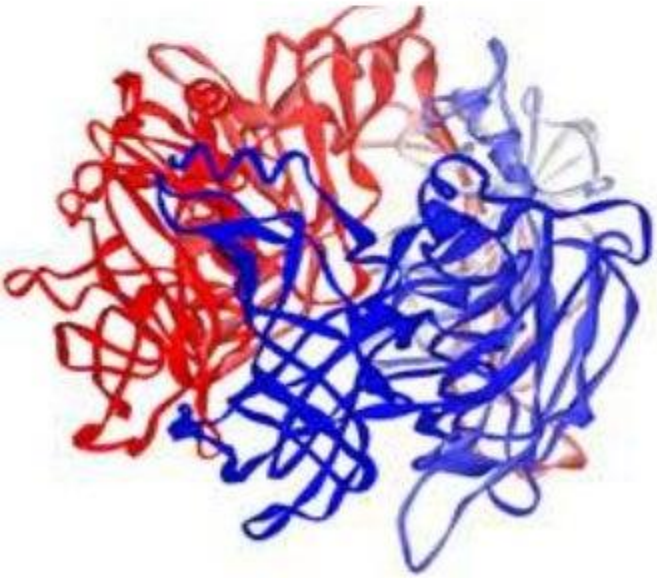
slow

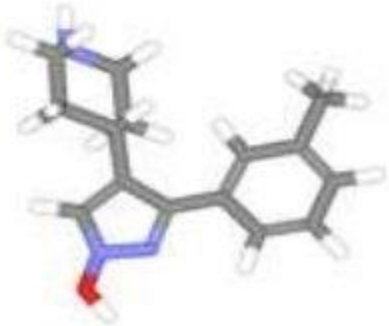
A single novel structure

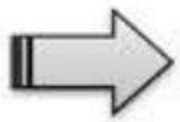
Automated Design

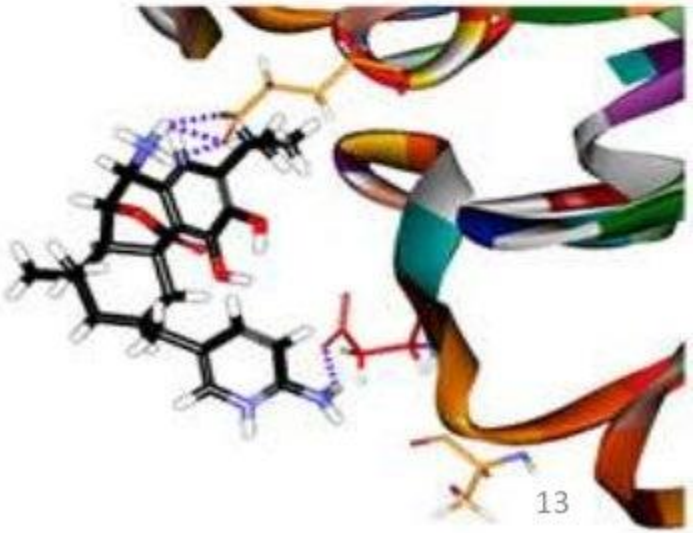
much faster

large numbers of diverse structures









Disadvantages

- The position of atoms in the crystal structure is accurate only to 0.2–0.4 A and allowance should be made for that.
- It is possible that the designed molecule may not bind to the binding site exactly as predicted.
- It is worth leaving scope for variation and elaboration of the molecule. This allows fine tuning of the molecule's binding affinity and pharmacokinetics.

Impotant Points In De Novo Drug Design

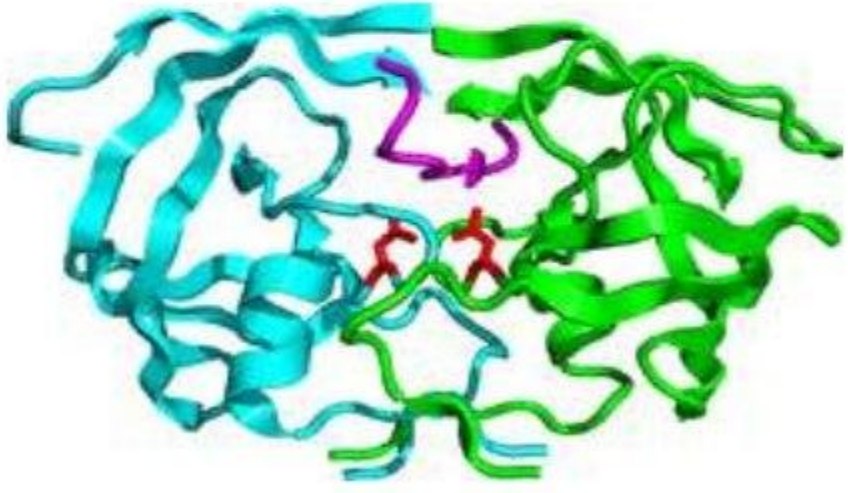
- Flexible molecules are better than rigid molecules.
- It is pointless designing molecules which are difficult or impossible to synthesize.
- Similarly, it is pointless designing molecules which need to adopt an unstable conformation in order to bind.
- Consideration of the energy losses involved in water desolvation should be taken into account.
- There may be subtle differences in structure between receptors and enzymes from different species. This is significant if the structure of the binding site used for *de novo* design is based on a protein that is not human in origin.

Problems of Automated De Novo

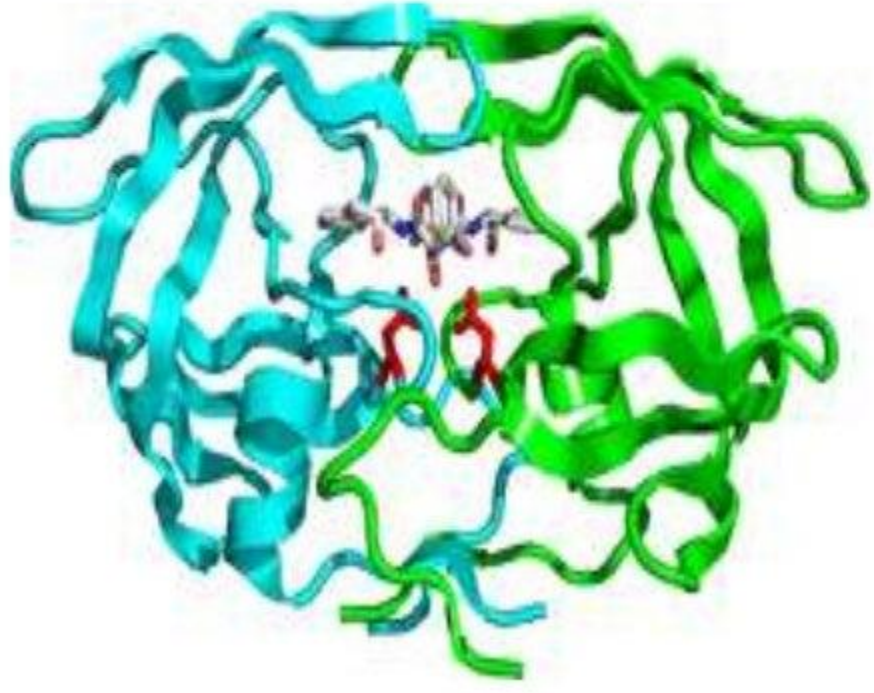
- automated *de novo* drug design is prone to generating structures which are either difficult or impossible to synthesize.
- automated *de novo* programs revolves around the scoring functions used to estimate binding affinities.

Applications

- Design of HIV 1 protease inhibitors
- Design of bradykinin receptor antagonist
- Catechol ortho methyl transferase inhibitors
- Estrogen receptor antagonist



Structure of enzyme



Enzyme with inhibitor

OTHER METHODS FOR DE NOVO DRUG DESIGN

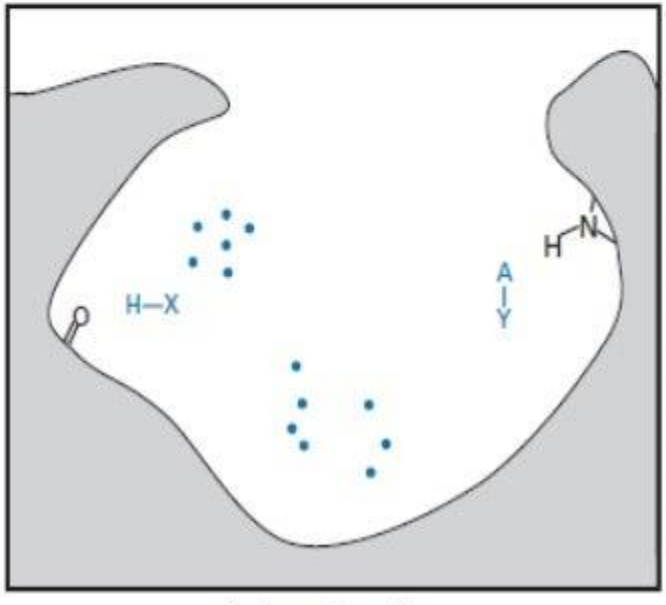
METHOD	PROGRAMS AVAILABLE
Site point connection method	LUDI
Fragment connection method	SPLICE, NEW LEAD, PRO-LIGAND
Sequential build up methods	LEGEND, GROW, SPORUT
Random connection and disconnection methods	CONCEPTS, CONCERTS, MCDNLG

LUDI

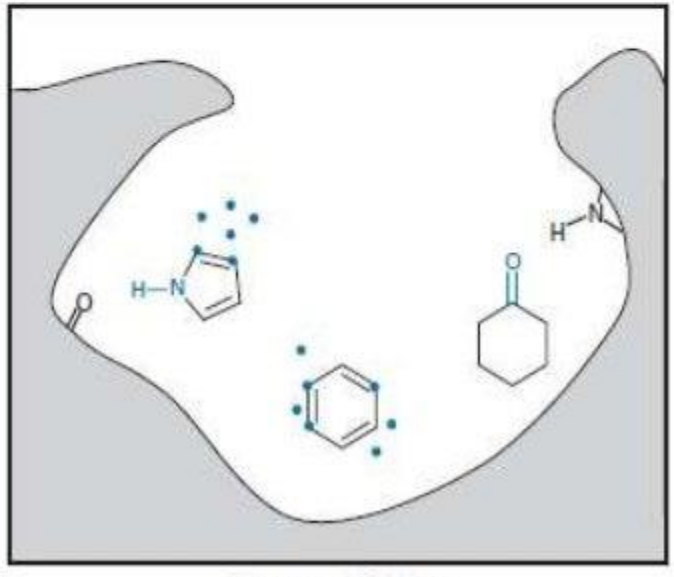
Stage 1: identification of interaction sites

Stage 2: fitting molecular fragments

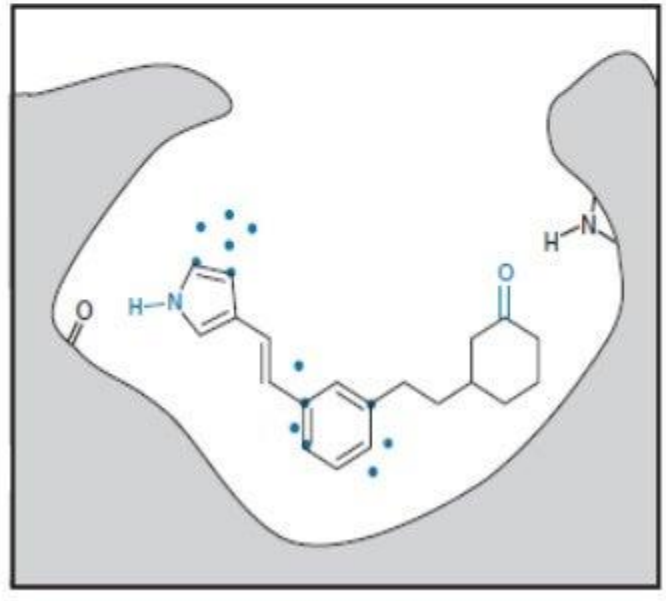
Stage 3: fragment bridging



Interaction sites



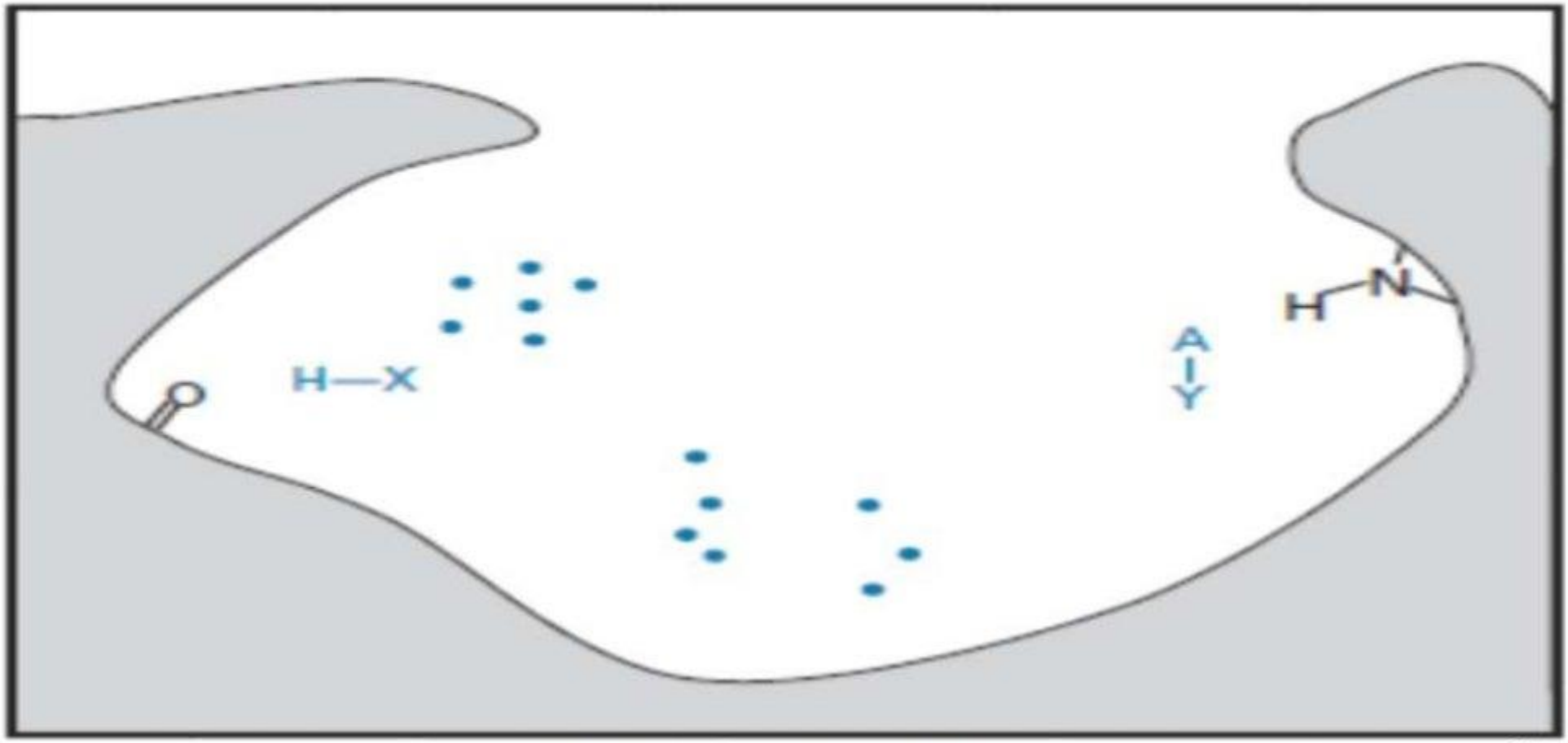
Fragment fitting



Bridging

Stage 1: Identification of interaction sites

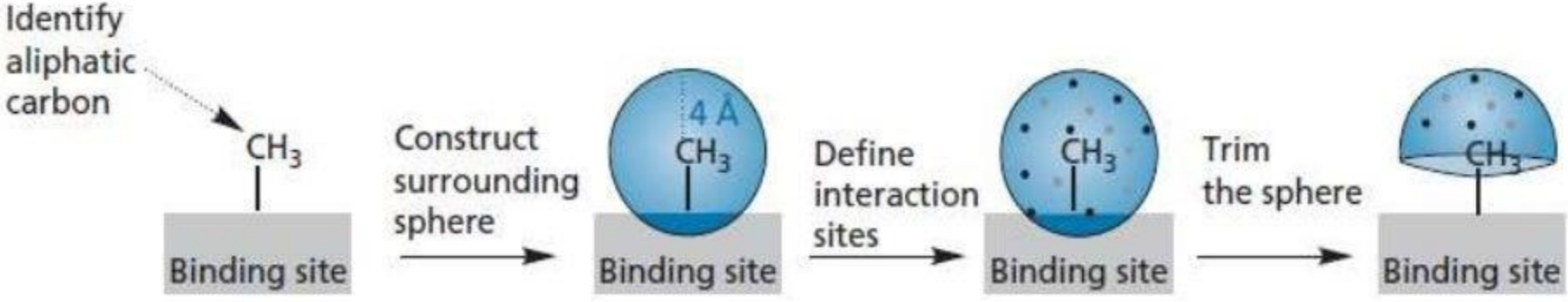
The atoms present in the binding site are analysed to identify those that can take part in hydrogen bonding interactions, and those that can take part in van der Waals interactions.



Interaction sites

Examples

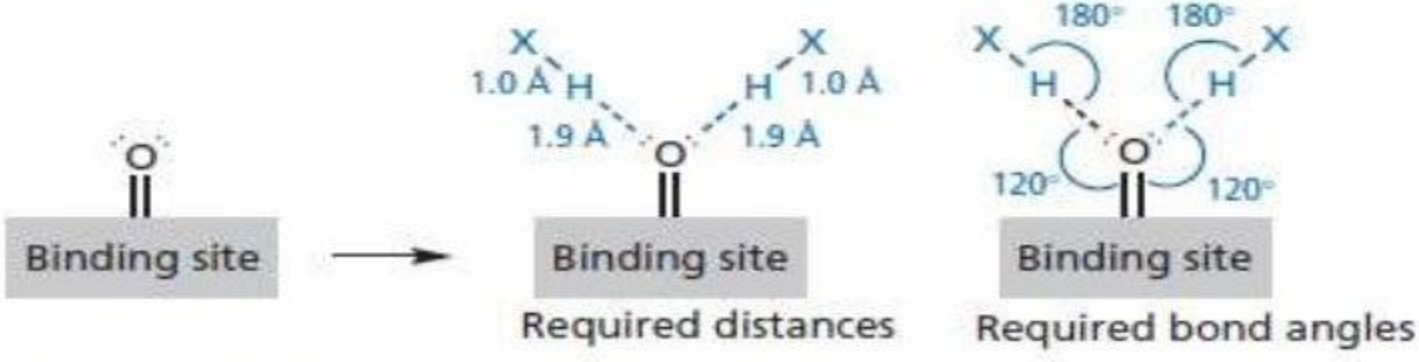
- The program would identify the carbon of that group as an aliphatic carbon capable of taking part in van der Waals interactions.
- This is a non-directional interaction, so a sphere is constructed around the carbon atom with a radius corresponding to the ideal distance for such an interaction(4 A).
- A number of points are placed over the surface of the sphere to define aliphatic interaction sites.
- Regions of the sphere which overlap or come too close to atoms making up the binding site are rejected.
- The remaining points are used as the aliphatic interaction sites.



Identifi cation of aliphatic interaction sites around a methyl group (LUDI).

Identifying interaction sites for hydrogen bonds is carried out in a different fashion.

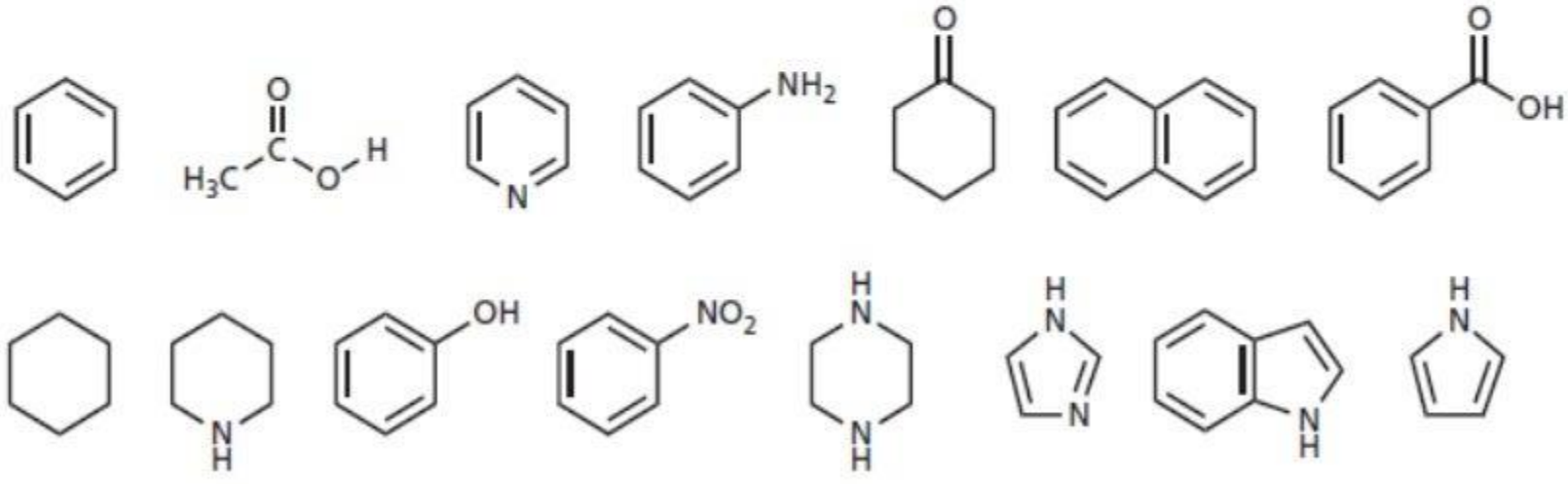
- As hydrogen bonds are directional, it is important to define not only the distance between the ligand and the binding region, but also the relevant orientation of the atoms.
- This can be done by defining the hydrogen bond interaction site as a vector involving two atoms.
- The position of these atoms is determined by the ideal bond lengths and bond angles for a hydrogen bond.



The interaction sites for a hydrogen bond donor, represented by H–X (LUDI).

Stage 2: fitting molecular fragments

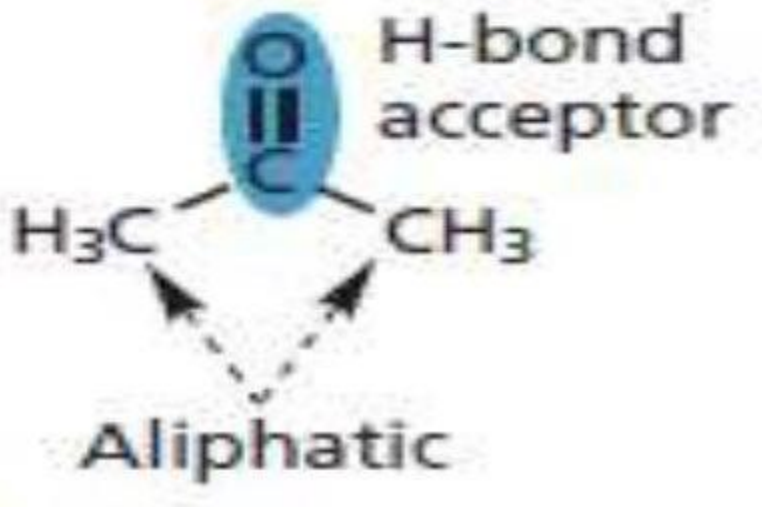
- The LUDI program accesses a library of several hundred molecular fragments.
- The molecules chosen are typically 5–30 atoms in size and are usually rigid in structure because the fitting procedure assumes rigid fragments.
- Some fragments are included which *can* adopt different conformations.



Examples of molecular fragments used by LUDI.

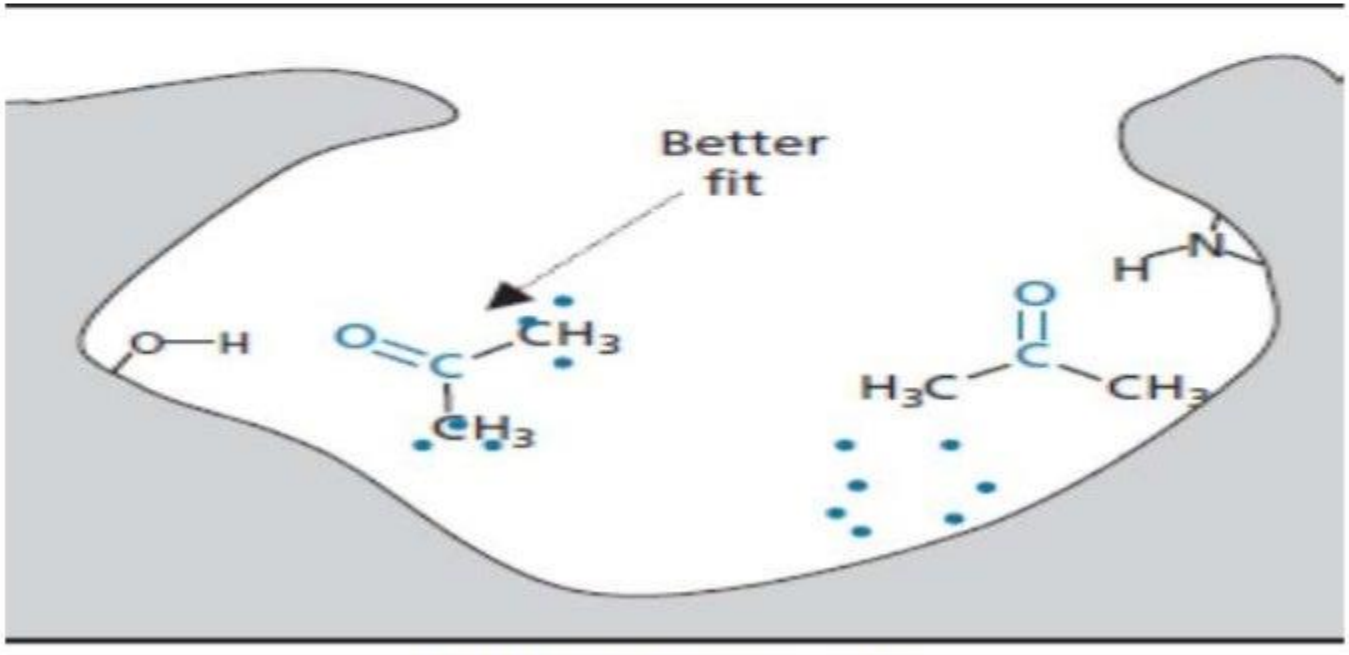
Examples

- The methyl carbons of an acetone fragment are defined as aliphatic and can only be fitted onto aliphatic interaction sites.
- The carbonyl group is defined as a hydrogen bond acceptor and can only be fitted onto the corresponding interaction site.



- Th e best fit will be the one that matches up the fragment with the maximum number of interaction sites.

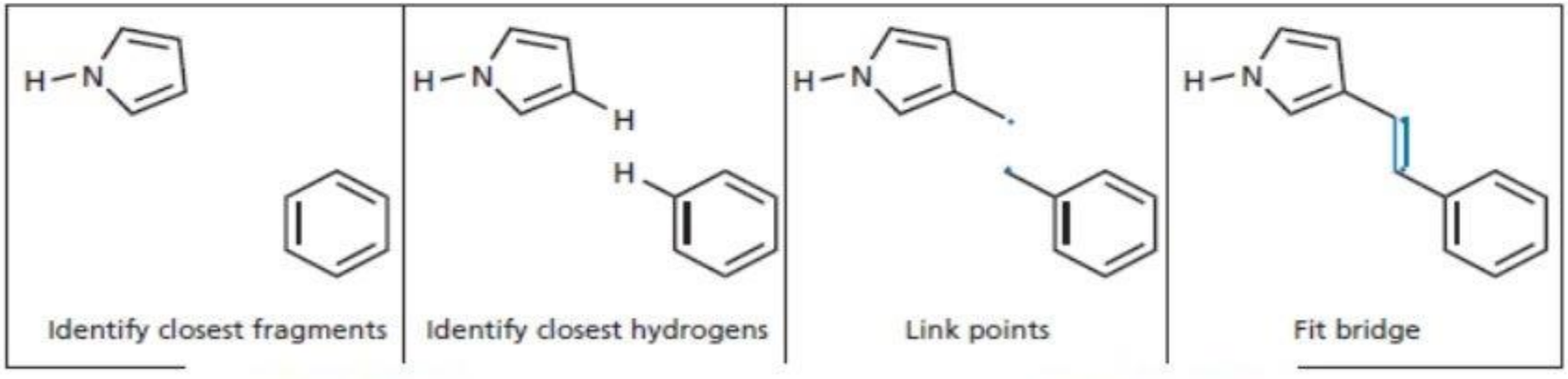
- The program can ‘try out’ the various fragments in its library and identify those that can be matched up or fitted to the available interactionsites in the binding site.



Fitting fragments

Stage 3: fragment bridging

- Fragments have been identified and fitted to the binding site, the final stage is to link them up.
- The program first identifies the molecular fragments that closest to each other in the binding site, then identifies the closest hydrogen atoms.
- These now define the link sites for the bridge. The program now tries out various molecular bridges from a stored library to find out which one fits best.
- A suitable bridge has been found, a final molecule is created.



The bridging process (LUDI).

SPROUT

- Like LUDI , the program fits fragments to interaction sites, but there are differences in the way that the process is carried out.
- Uses **templates** to represent molecular fragments.
- Each template is defined by vertices and edges, rather than by atoms and bonds.
- A vertex represents a generalized sp-, sp2, sp3 hybridized atom.
- An edge represents a single, double, or triple bond, depending on the hybridization of the vertices at either end.

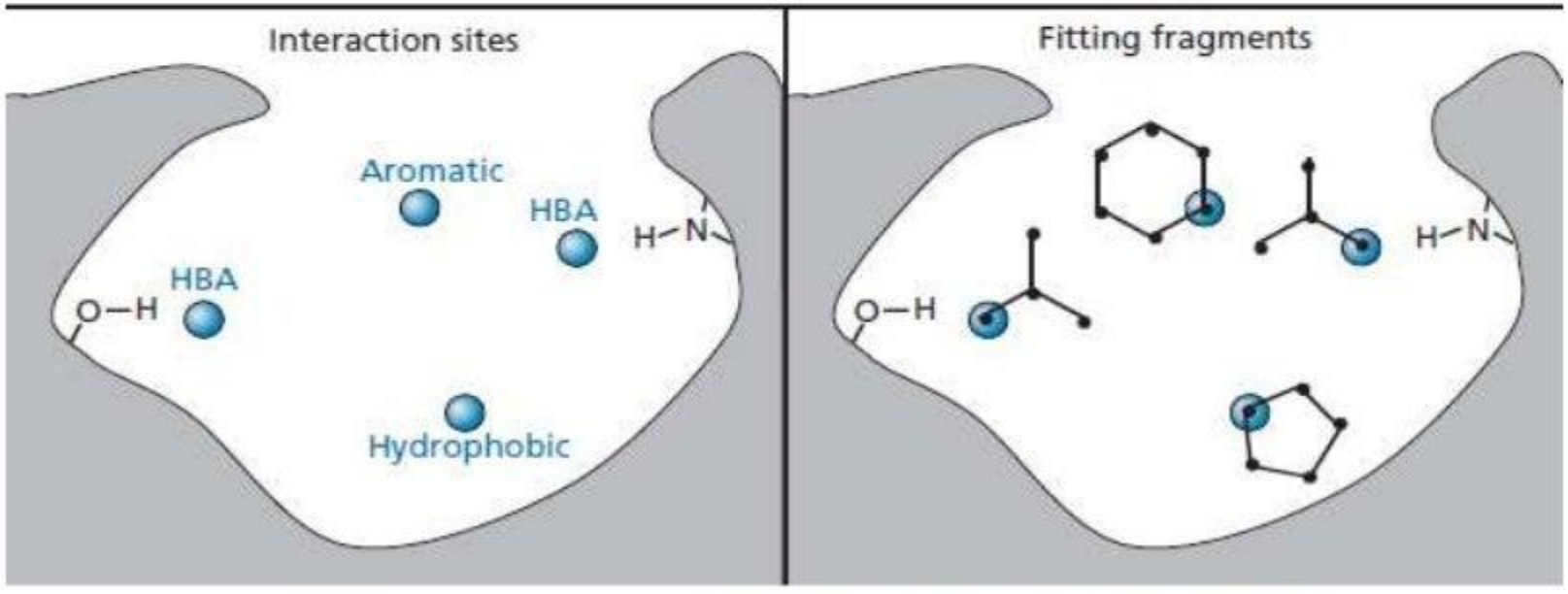
Fragment template

Examples of structures represented by a template used in SPROUT.

Stages of the generation of the structures

1- Generate fragment templates that will fit the binding site.

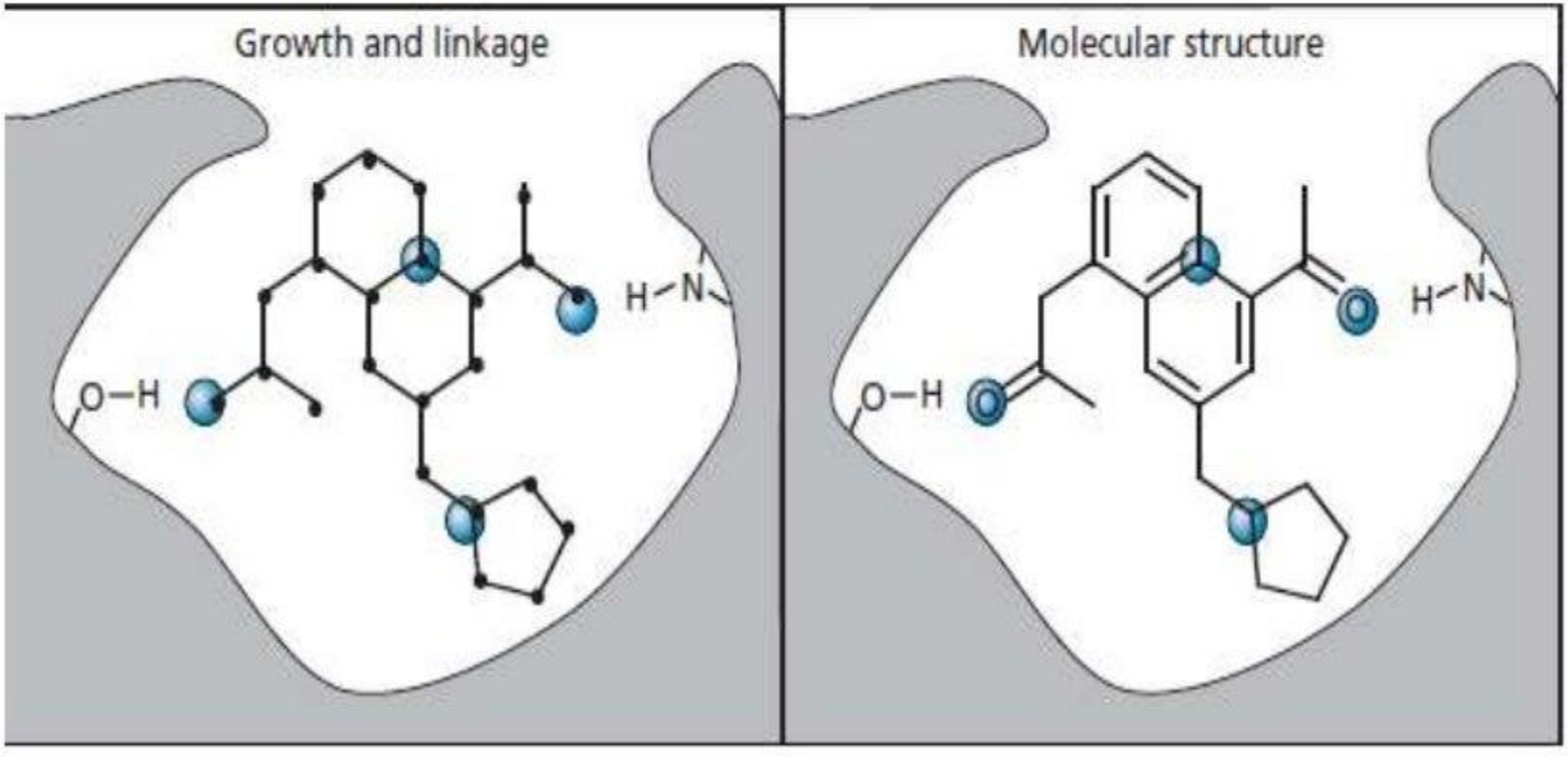
The program selects a fragment template randomly and positions it into the binding site by placing one of the vertices at the center of a sphere.
Fragment templates are placed at all the spheres and grown towards each other until they are finally linked.



Generating structures using SPROUT.

2- Create specific molecules from the molecular templates that have been produced.

This involves replacing the vertices with suitable atoms to allow favourable hydrogen bonding and vander waals interactions whith the binding site.



Generating structures using SPROUT.

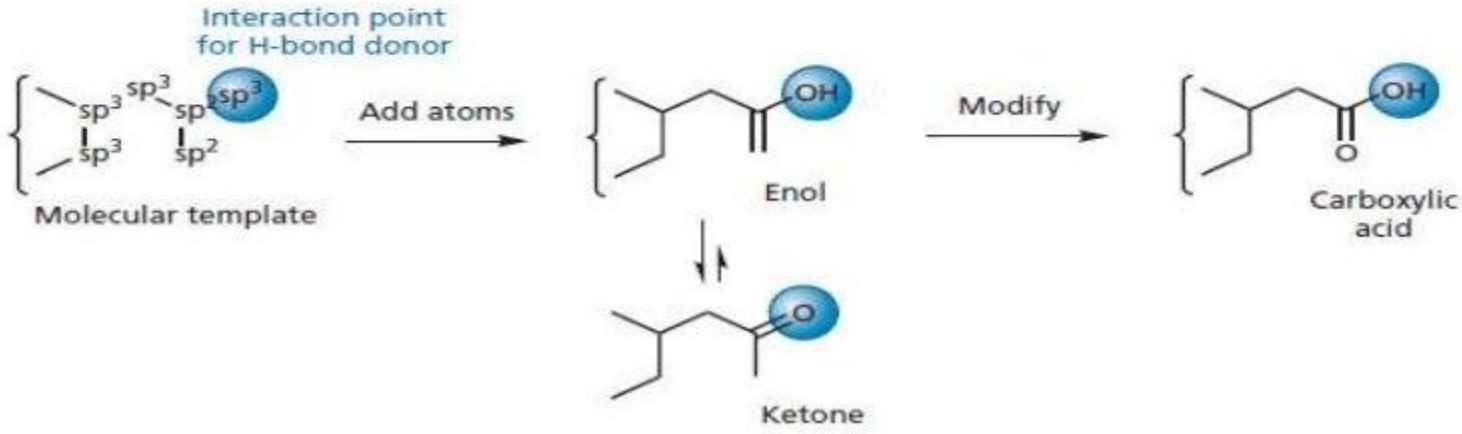
- It radically cuts down the number of different fragments that have to be stored in the program, making the search for novel structures more efficient.

- The growth of fragment templates allows a molecular template to be constructed which bridges interaction sites that are some distance apart.

In the **LUDI** methode, single fragments are placed at each interaction point and are then linked. If there is a large seperation between the interaction sites, there might not be a sufficiently long linker to connect the fragments.

- Sprout has the capacity to identify certain structural features that might be unrealistic and then modify them.

For example, an OH might be generated during the second stage in order to introduce a hydrogen bond donor, but if the OH is linked to a double bond this results in an enol which would tautomerize to a ketone. The latter would not be able to act as a hydrogen bond donor. The programme can identify an enol and modify it to a carboxylic acid which can still act as a hydrogen bond donor.



Modification of an enol to a carboxylic acid by SPROUT.

Advantage

- The programe also has the ability to modify structures such that they are more readily synthesized.

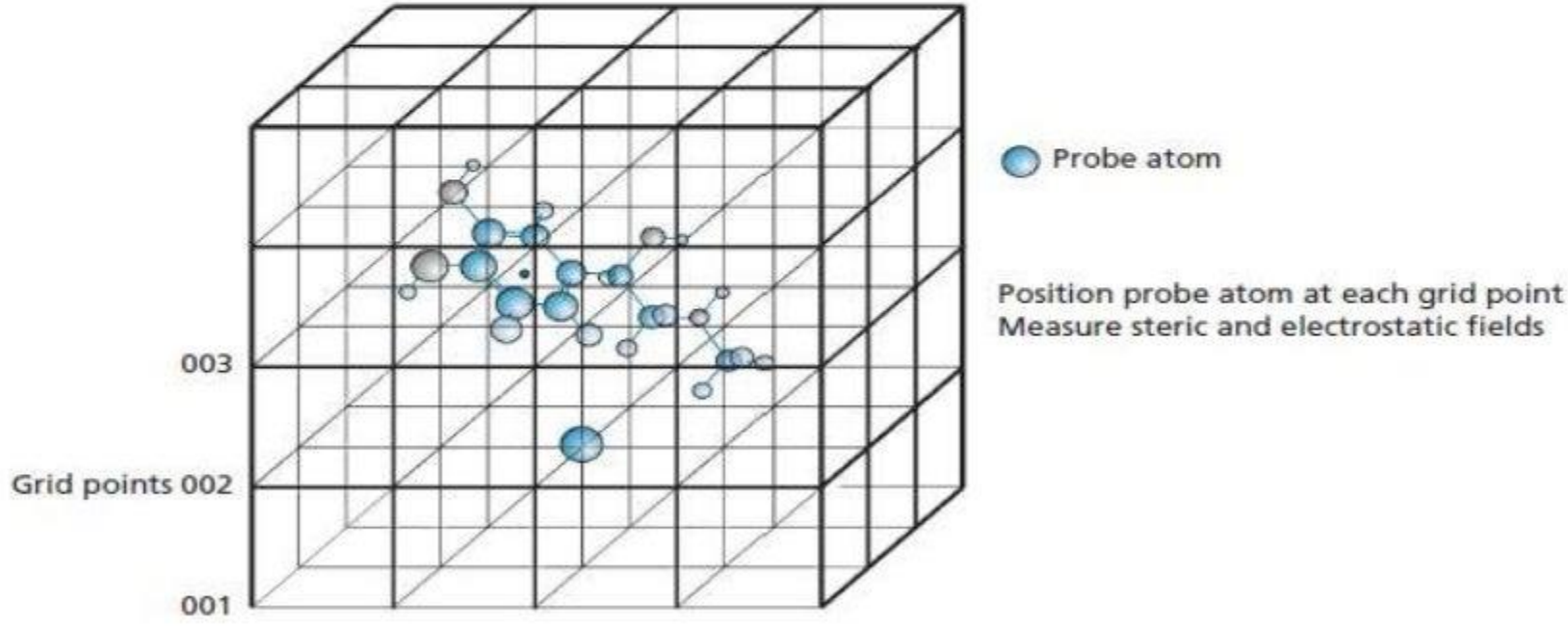
For example, introducing a heteroatom into a two-carbon link between two rings generates a structure which can be more readily synthesized.

Modification by SPROUT to generate a more synthetically feasible structure.

- The strucures that are finally generated by **sprout** are then evaluated in silico for a variety of properties, including possible toxicity and pharmacokinetic properties.

LEGEND

A grid is set up within the binding site to identify steric and electrostatic interaction energies between each grid point and the binding site.



Measuring fields around a molecule by placing a probe atom at grid points.

- These are tabulated for different types of atom and are used to estimate vander waals interactions for the growing skeletons that are generated by the program, as well as for structure optimization of final structures.

- The operator has the choice of starting from a single heteroatom, placed in such a position that it can form a hydrogen bond with the binding site.

DIFFERENCE

Unlike LUDI and SPROUT, LEGEND does not use fragments or templates to generate skeletons.

GROW

It is a program that uses molecular fragments to generate novel ligands for binding sites. The fragments used represent aminoacides and so the structures that are generated are limited to peptides.

SYNOPSIS

It is designed to generate synthetically feasible structures. Fragments can only be linked if there is a known reaction which will allow it.

CONCLUSION

- Although a relatively new design method, de novo design will play an ever-increasing role in modern drug design. Though yet not able to automatically generate viable drugs by itself, it is able to give rise to novel and often unexpected drugs.
- Rather slow and inefficient.

- Ignores synthetic feasibility while constructing structures.

- Cannot be a sole basis for drug design.

- The number and variety of structures which could be identified are limitless and so the chances of hitting the ideal structure are poor.

- There is far more to drug design than finding structure that binds strongly to its target.

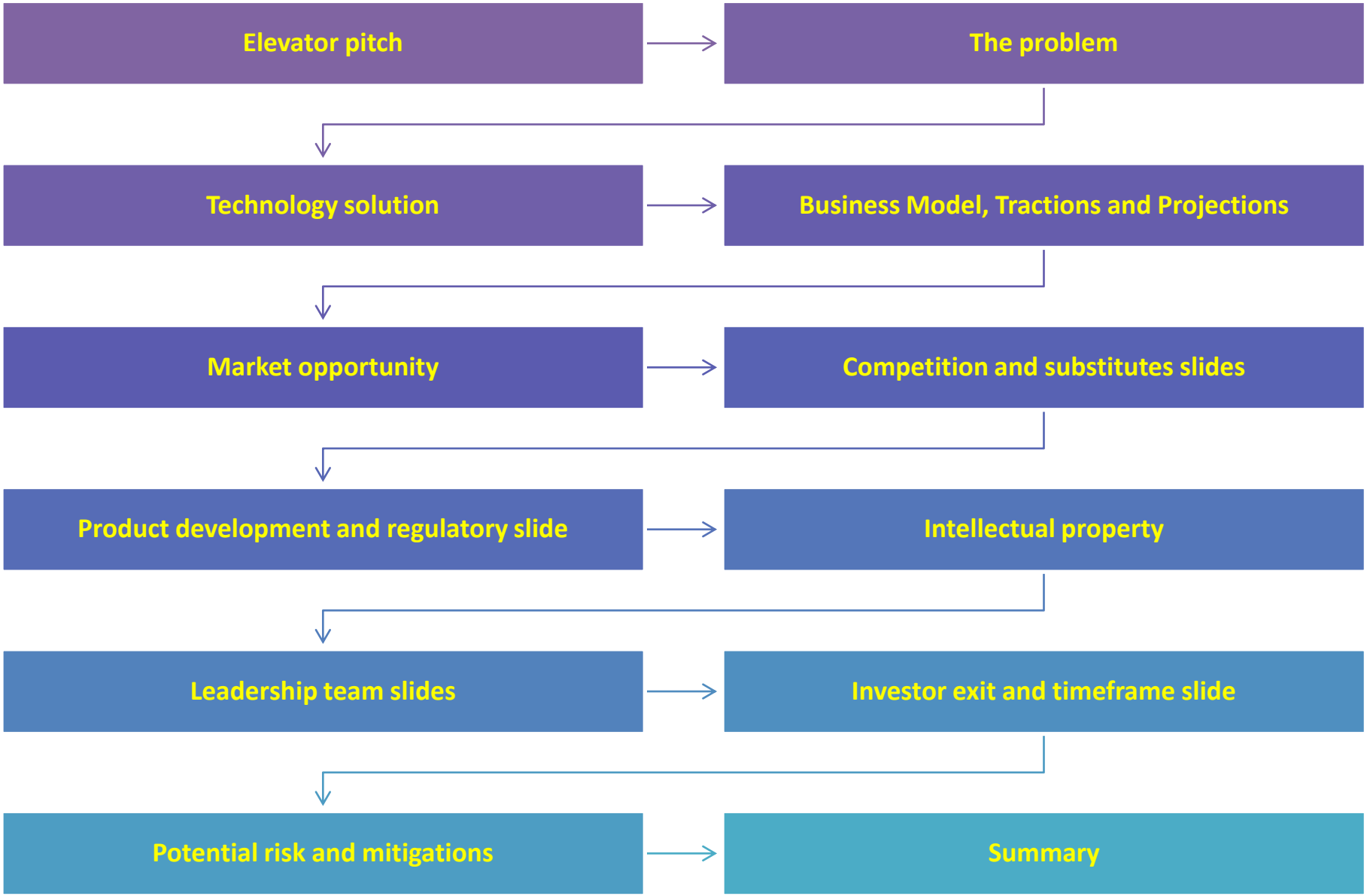
- It does not identify whether the structures identified will have favourable pharmacokinetic properties or acceptable safety profiles.

- It can stimulate new ideas and identify novel lead structures which could then be optimized through structure-based drug design.

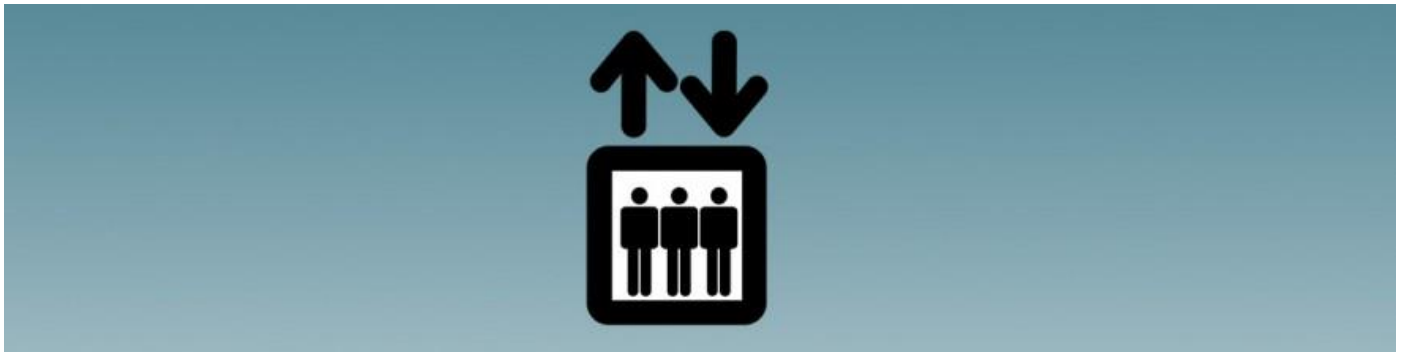
Thank You!

How to pitch to an INVESTOR

Investor pitch-Outline



• Elevator pitch



- Deliver a short summary of your project within the time it takes for an elevator ride, so about 30 seconds.
- Challenging right? You have a mere 30 seconds to hook the investor and convince them that your idea is worth their time.
- Experienced investors will weed out good ideas from the bad ones within the first minute so keep it simple and captivating.

• The Problem

- The Problem:The better that investors understand and agree with the significance of the problem

• Technology and Product “Solution” Slide

- How does your technology/product application specifically solve the problem
- Show Data! – nothing substitutes for plenty of evidence (data) that your proposed product can work – Show experimental results, prototype testing results, external or independent testing results mechanism- of-action

• Market Opportunity/Strategy

- Show how big the market is in dollars/INR

• Business Model, Tractions and Projections

- Describe how will you make money – Are you going to sell the end product or are you an intermediary?
- Show how you will reach your customers – Will you need distributors

• Competition and Substitutes Slide

- Describe the current and future competition for your proposed product
- What are your product's points-of-differentiation compared to the competition or substitutes for your product

• Product Development and Regulatory Slide

- Describe your current product development stage and what has been accomplished to date
- Describe the product development milestones and the timeframe you expect to reach these
- Briefly discuss the regulatory pathway for approval

• Intellectual Property

- Discuss your issued patents
- If IP is licensed, describe the terms

• Leadership Team Slide

- Describe the current senior management team and their relevant background information
- Show who are your advisors

• Investor Exit and Estimated Timeframe Slide

- Potential Exit and Timing (Do you anticipate a potential IPO or an acquisition)?
- If acquisition, list your top 3 potential acquirers
- Share how long you anticipate it may be before an investor exit

• Potential risks and mitigations

- Any critical technology development risks
- All regulatory issues and risks for your particular product
- Major market issues for acceptance of your product

• Summary

- Summarize the points you want the audience to remember when they walk away
- The novelty of your technology and the unique opportunity of your product

Entrepreneurship

Dr. Fels Saju
Associate Professor
Nirmala College of Pharmacy
Muvattupuzha

INHIBITIONS

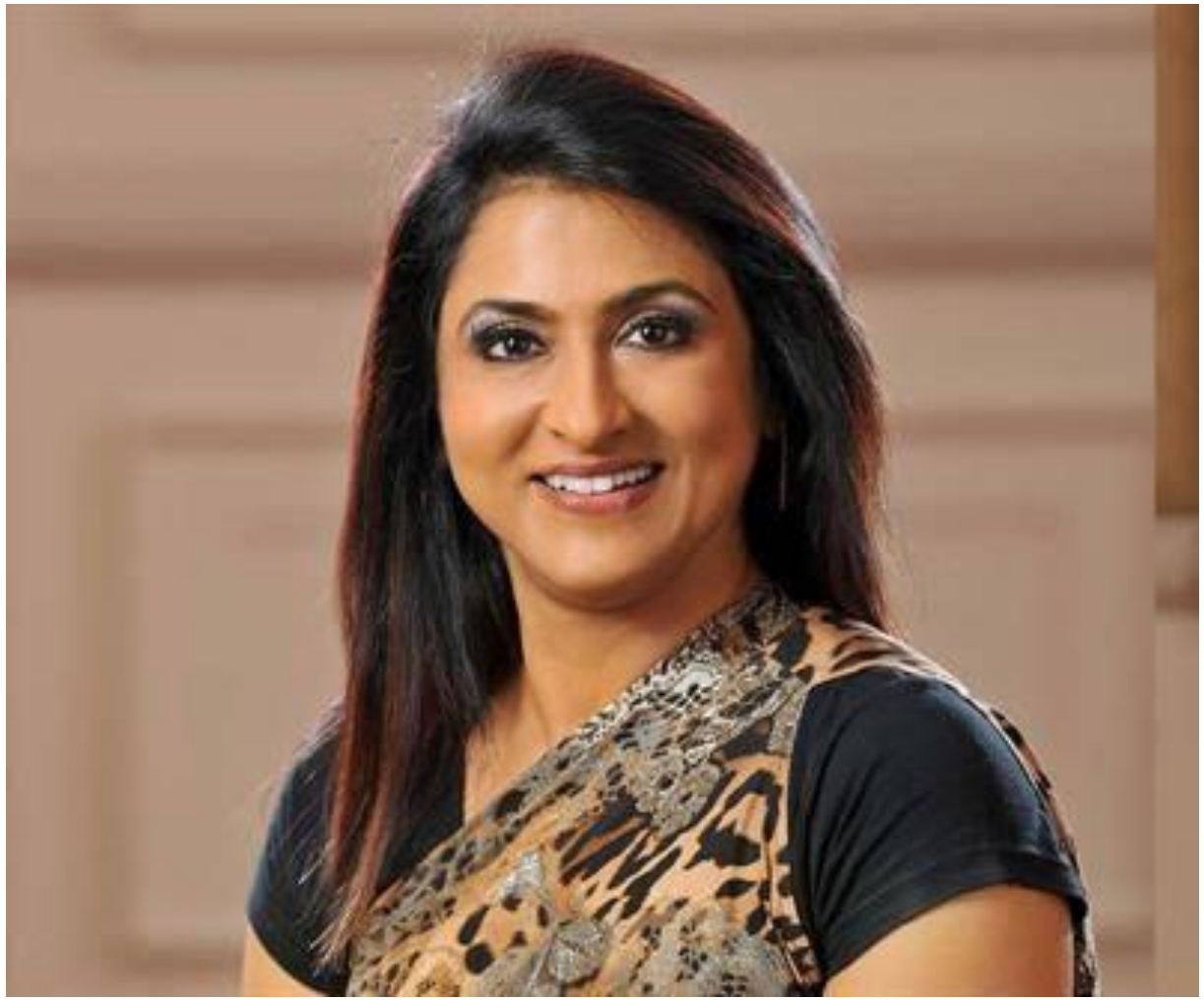
AGE ……. ???

RITESH AGARWAL

EDUCATION….. ???

LAKSHMI PRASAD

SEX…????



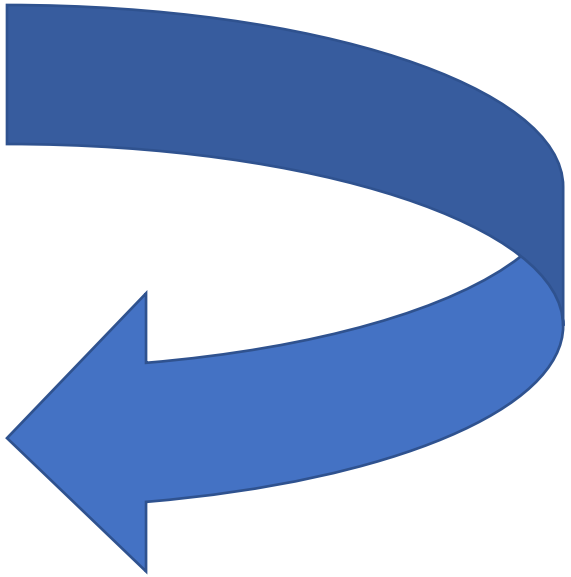
BEENA KANNAN

FAMILY BACKGROUND

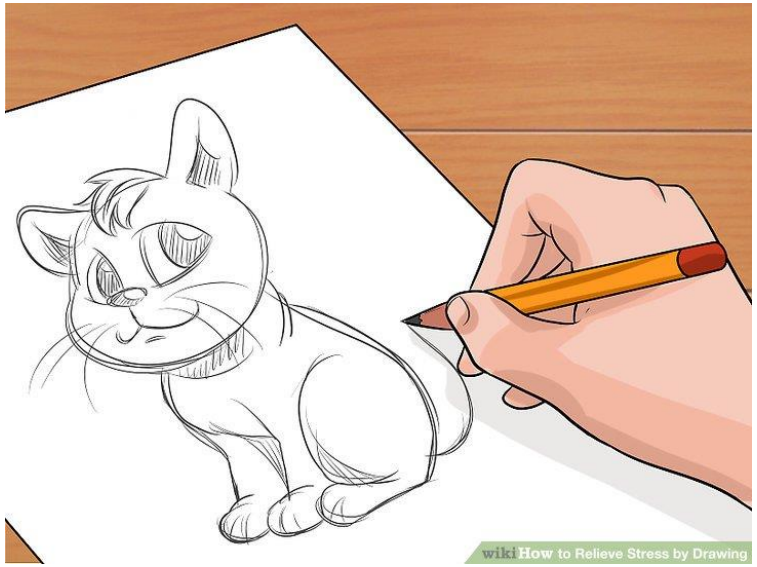
Qualities

Unlimited DREAMS

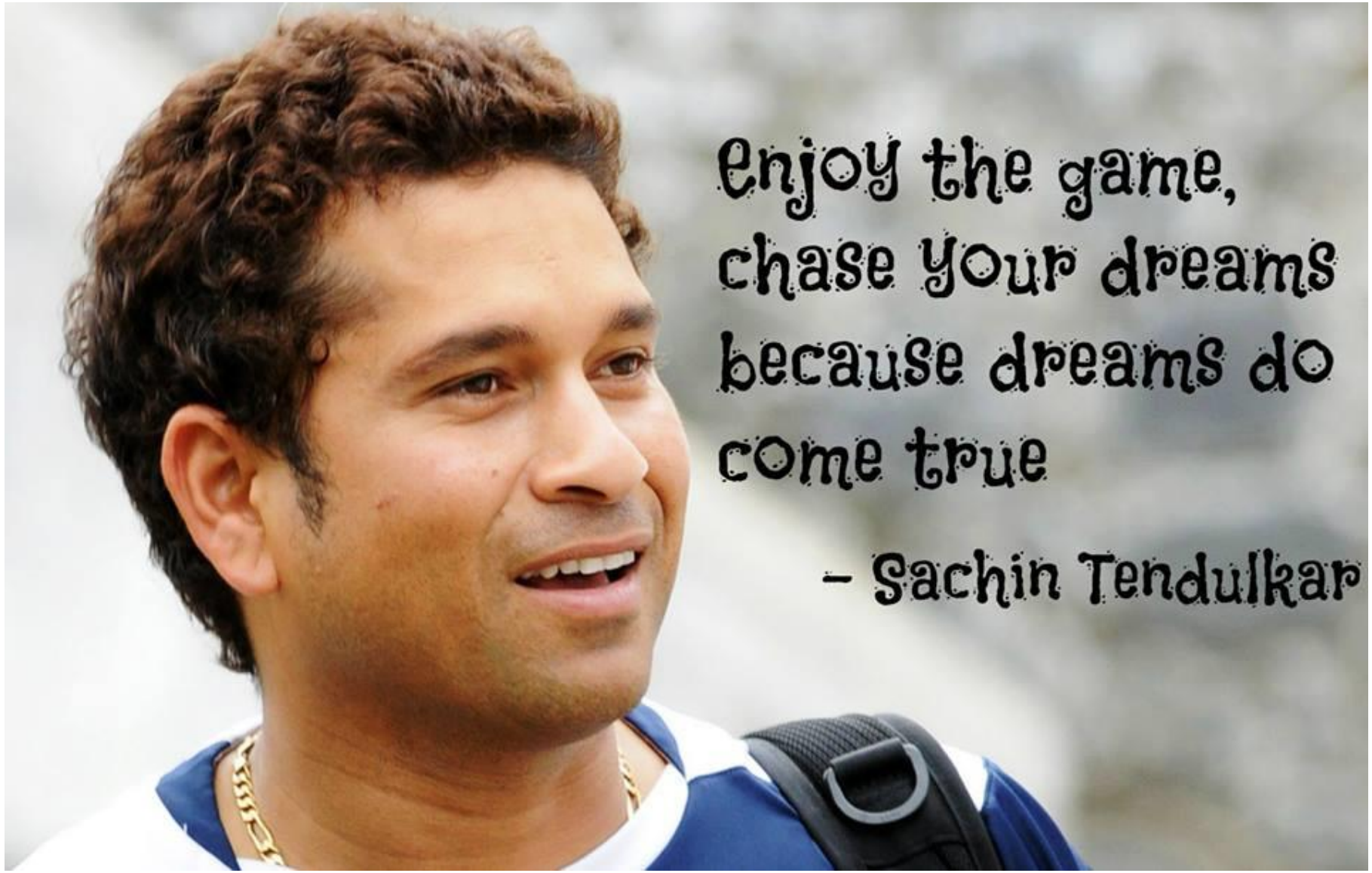

EMPIRE
VIDEO
EMPIRE



IDENTIFY YOUR **PASSION**


wikiHow to Relieve Stress by Drawing

Blend your dreams with passion


Enjoy the game,
chase your dreams
because dreams do
come true
- Sachin Tendulkar

Why Entrepreneurship ??

Top 10 Indian Startups 2020

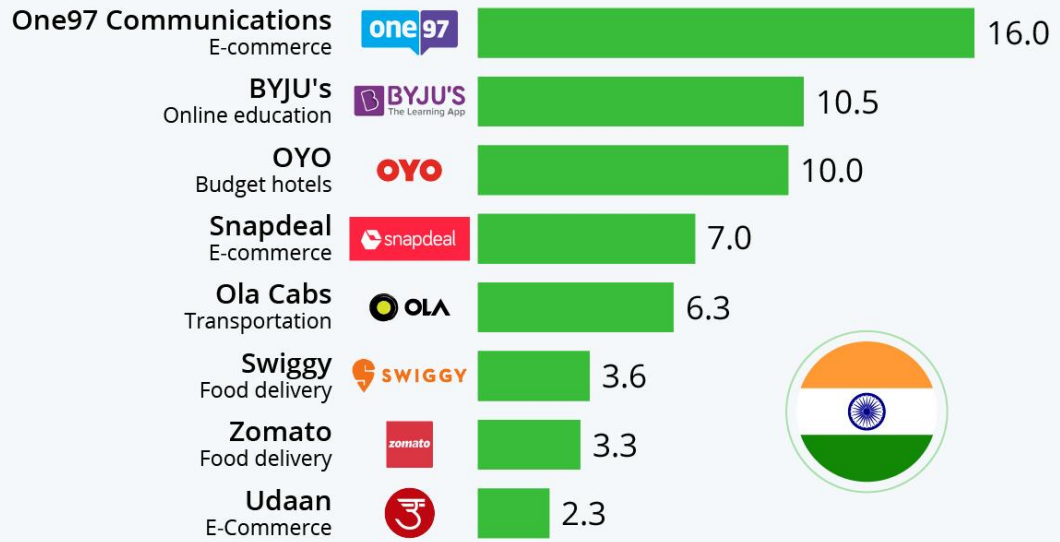
Company	Industry	Funding (US $)
1. One97 (Paytm)	Commerce and Shopping	4.4 B
2. Ola Cabs	Transportation	3.8 B
3. OYO	Travel and Tourism	3.2 B
4. ReNew Power	Energy	2.8 B
5. Snapdeal	Commerce and Shopping	1.8 B
6. Swiggy	Food and Beverage	1.6 B
7. BYJU'S	Education	1.4 B
8. BigBasket	Commerce and Shopping	1.1 B
9. Delhivery	Logistics	935 M
10. Zomato	Food and Beverage	915 M

Source: Crunchbase May 2020

DISFOLD

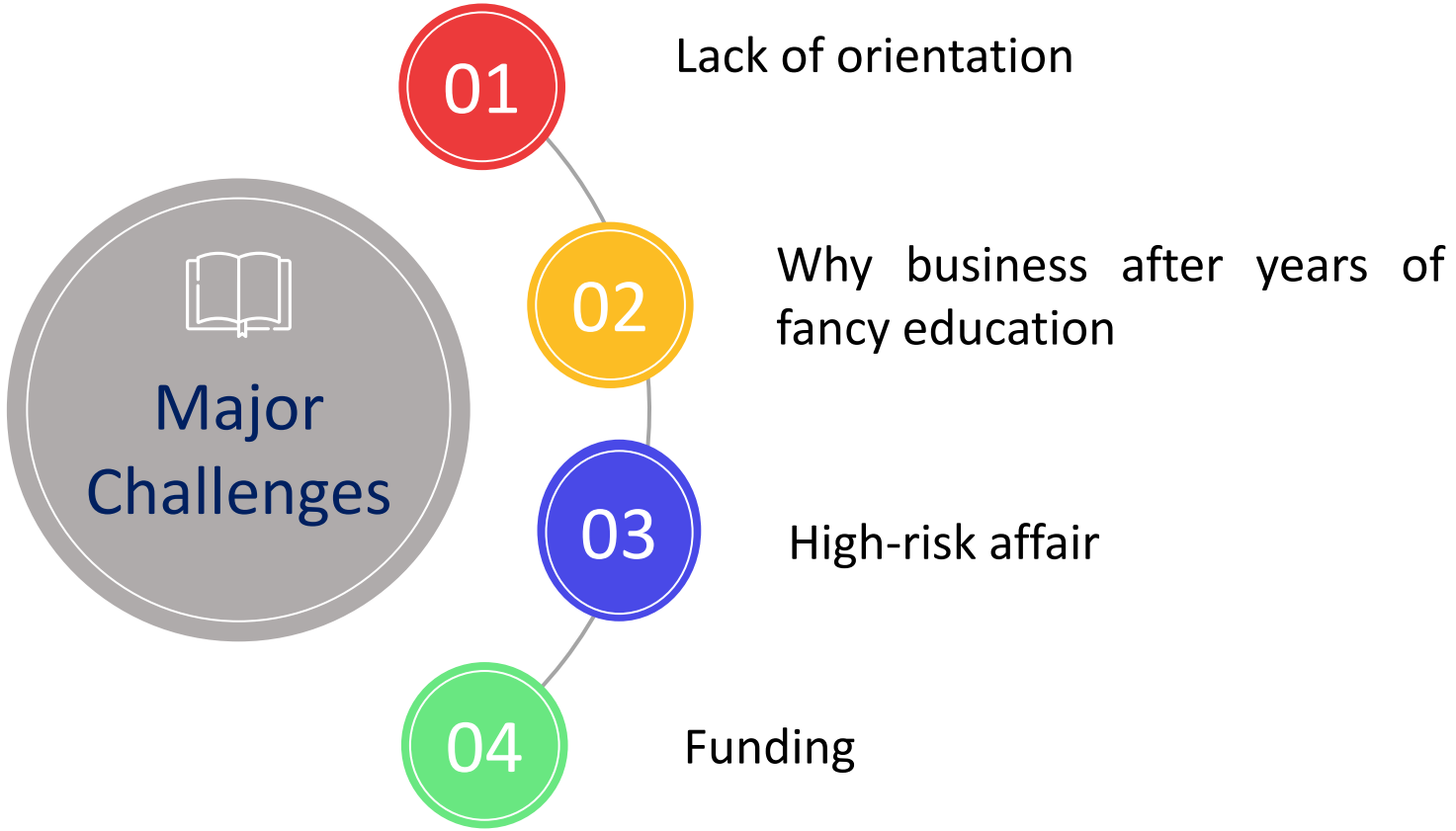
The Highest-Valued Startups in India

Startups with the highest valuations in India in 2020 (in billion U.S. dollars)



As of June 2020
Source: CB Insights

statista


Major Challenges
01
Lack of orientation
02
Why business after years of fancy education
03
High-risk affair
04
Funding

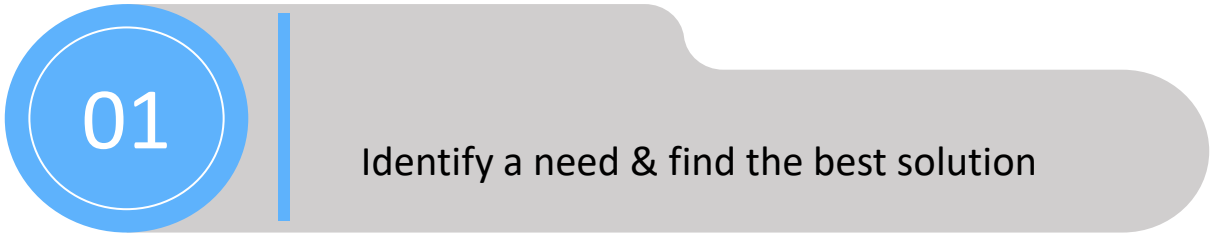
Steps in Entrepreneurship Process

01 Identify a need & find the best solution

02 Feasibility Analysis

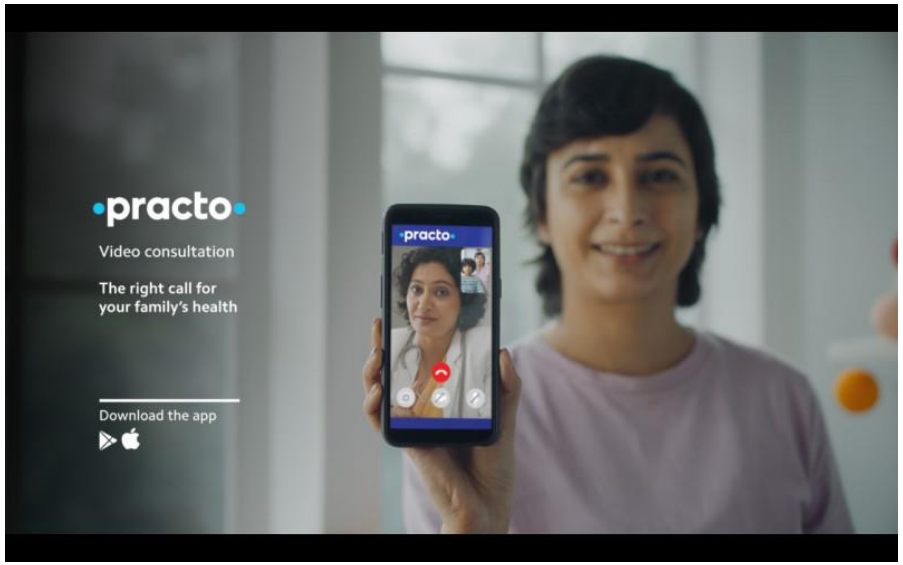
03 Funding

Steps in Entrepreneurship Process




OLA
OLA

UBER

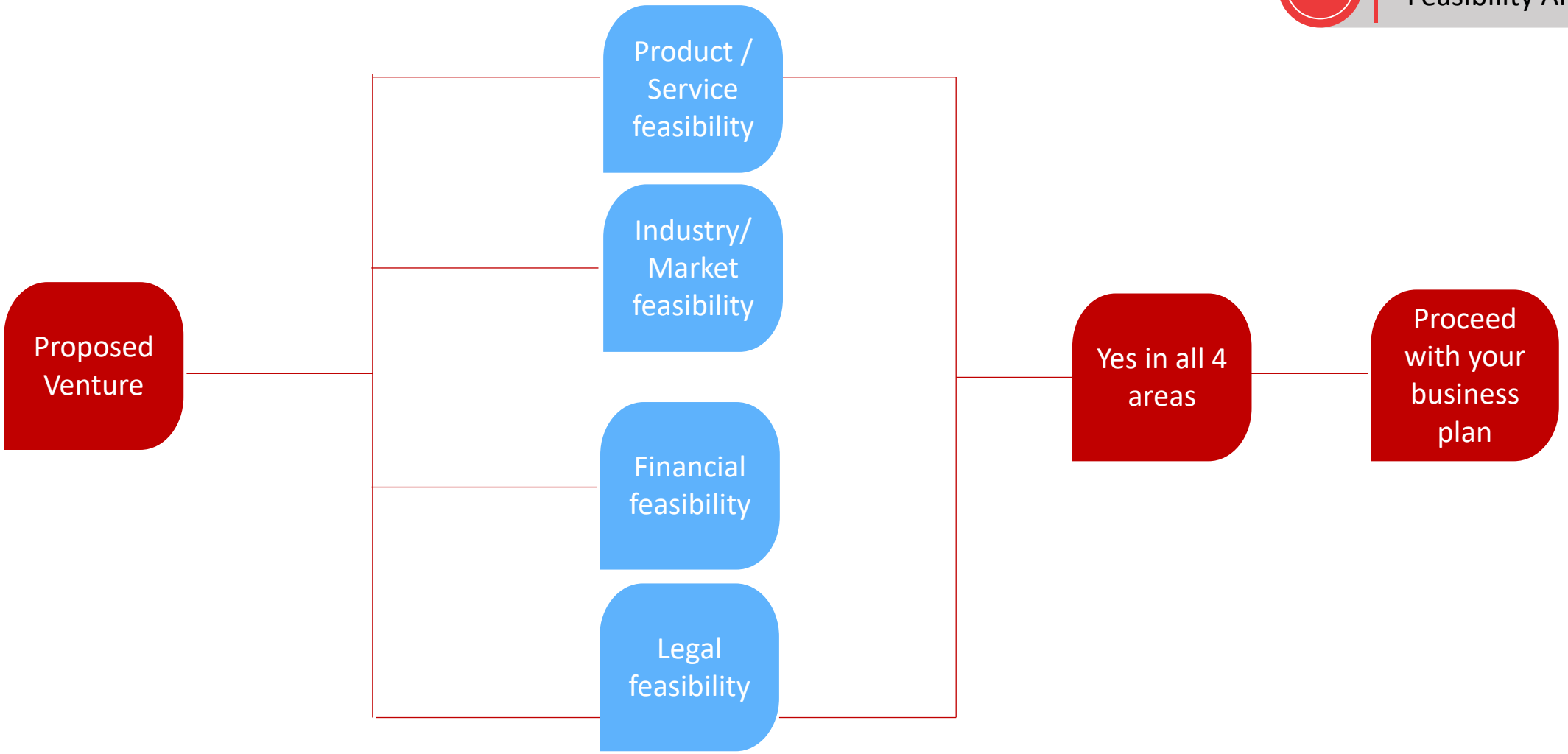

practo
Video consultation
The right call for
your family's health
Download the app
practo

Steps in Entrepreneurship Process

02

Feasibility Analysis

Assessing achievability of the endeavor


Proposed Venture
Product / Service feasibility
Industry/ Market feasibility
Financial feasibility
Legal feasibility
Yes in all 4 areas
Proceed with your business plan

01 Product/Service feasibility

Concept Testing

- Check the acceptance of the product / service being offered
- Benefits of the product / service

Usability testing

Users of the product will be asked to perform certain tasks with the product

Helps to assess

- Products ease of use
- Users' perception of the experience
- Drawbacks

02 Market feasibility

a. Industry attractiveness

Check whether it is Saturated industry / New industry

Growth potential

Primary and secondary research

Primary research – collected by entrepreneur by talking to potential customers and key industry participants

Secondary research - industry related publications, government statistics, reports from research firms

b. Identification of Niche market

Segment of a larger market that can be defined by its own unique needs, preferences or identity that makes it different from the market at large

c. Current demand analysis

Market survey →

Demographic & Sociological information: Age, gender, income, residence, religion, customs, beliefs and social background

Attitudinal information: preferences, intentions, attitudes, habits and responses

Analysis
- Target market
- Barriers to entry

d. Future demand forecasting

Qualitative Methods: Jury of executive opinion methods and Delphi method

Quantitative methods : Time-series method and casual methods

03 Financial Feasibility

a. Cost of project

Land, site development, buildings and civil works
Plant and machinery
Preliminary and capital issue expenses
Working capital
Initial cash losses
Salary and employee welfare
Insurance

b. Means of finance

Share capital

Term loans

Debenture capital

c. Project profitability

- Ability to generate financial profit or gain from the project.
- it is calculated by the cost-income ratio.

d. Break even point

Total Sales = Total expenses

Break-even is a situation where an organisation neither makes money nor loses money, but all the costs are covered.

04 Legal feasibility

- Copyrights or patent laws
- Trust/company laws
- Labor regulations
- Environment laws

Steps in Entrepreneurship Process

Funding

Self funding

Advantages

Financial control

Creative freedom

Chance to prove business model

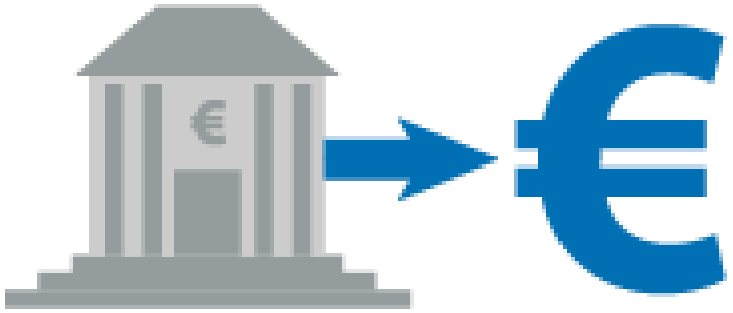
Disadvantages

Personal risks

Slower growth

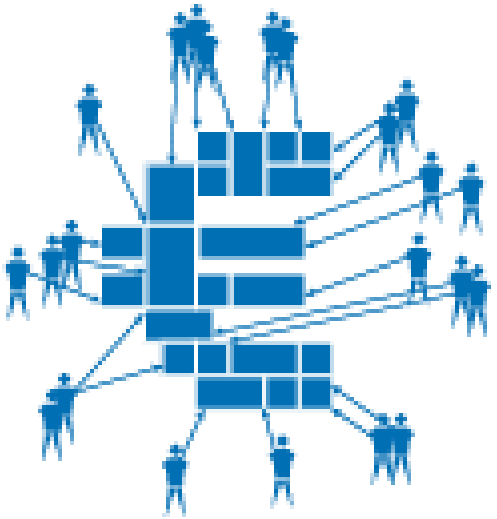
b Crowdfunding

TRADITIONAL FUNDING

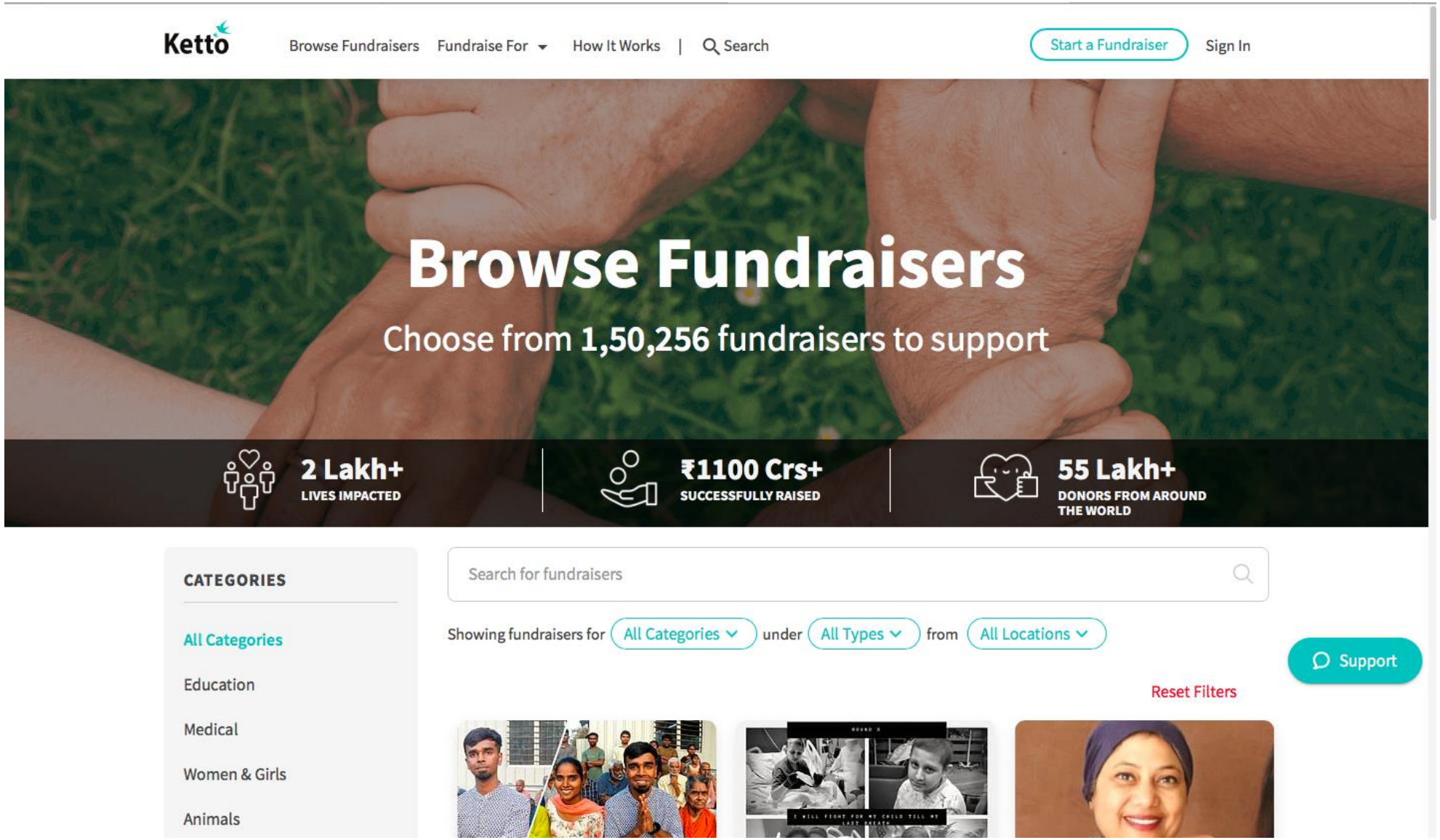


Large amounts from one,
or a few, sources

CROWDFUNDING



Many small sums from
a large group of individuals


Ketto
Browse Fundraisers
Fundraise For
How It Works
Search
Start a Fundraiser
Sign In
Browse Fundraisers
Choose from 1,50,256 fundraisers to support
2 Lakh+
LIVES IMPACTED
₹1100 Crs+
SUCCESSFULLY RAISED
55 Lakh+
DONORS FROM AROUND THE WORLD
CATEGORIES
All Categories
Education
Medical
Women & Girls
Animals
Search for fundraisers
Showing fundraisers for
All Categories
under
All Types
from
All Locations
Reset Filters
Support

Catapooolt
Let's start the Next

How it works | Start a Campaign | Explore | Login | INR

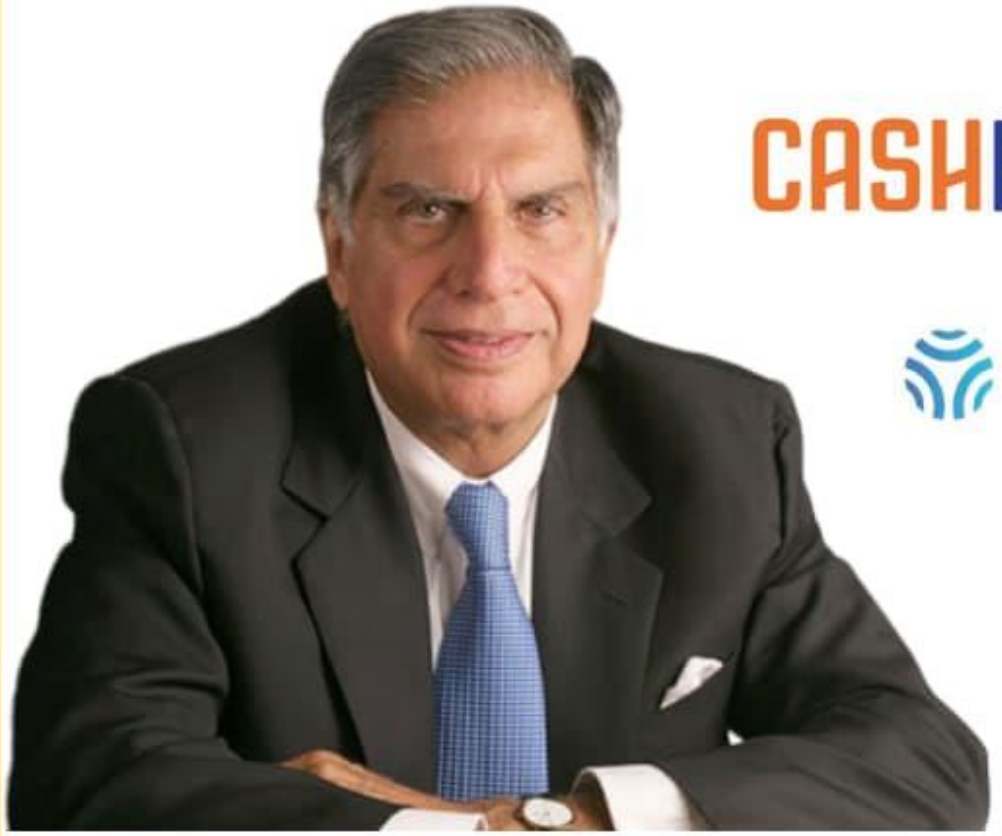
CATAPOOOLT BRINGING INNOVATION TO LIGHT BY CROWDFUNDING HOLOSUIT

(World's first consumer friendly, bi-directional, full body motion controller with haptic feedback,that received Angel Investment by Crowdfunding on Catapooolt)

Generic | Super Solvers Challenge | Product Czars | Changemakers | Gamechangers

C Angel investors

- Individuals with surplus cash
- keen interest to invest in upcoming startups.
- They also work in groups of networks to collectively screen the proposals before investing.



CASHKARO.COM

OLA

climacell

CarDekho

DogSpot.in

cure.fit

MOST ACTIVE ANGEL INVESTORS

Half of the top angels are entrepreneurs.

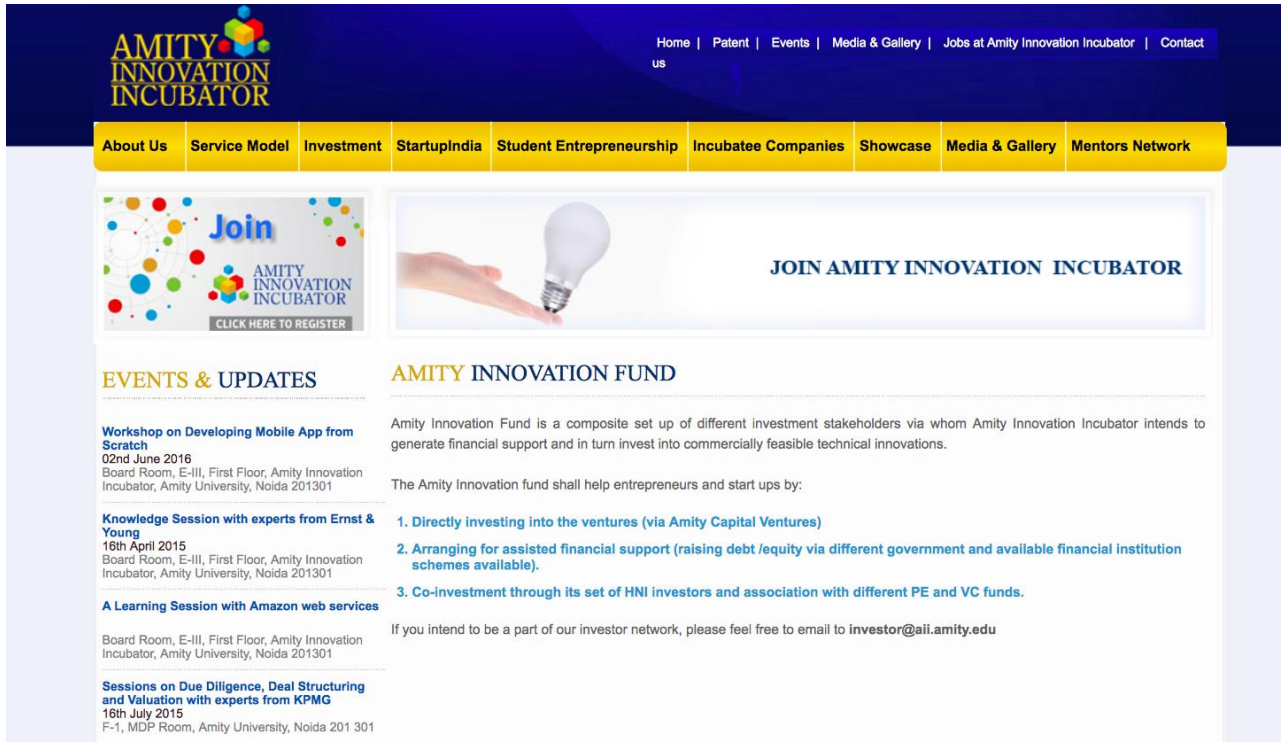
NAME	PROFILE	NO. OF DEALS
Ratan Tata	Chairman Emeritus, Tata Sons	18
T V Mohandas Pai	Chairman, Manipal Global Education Services	18
Kunal Bahl	CEO, Snapdeal	15
Rajan Anandan	MD, Google India & Southeast Asia	15
Rohit Bansal	Co-founder, Snapdeal	15
Zishaan Hayath	Founder, Toppr	12
Anupam Mittal	Founder CEO, People Group	12
Binny Bansal	Co-founder, Flipkart	10
Ajeet Khurana	Independent angel investor	9
Vikram Chachra	Founding partner, Eight innovate	9

Infographic: Bhakti Nair **Source:** VCCEdge

d Venture capitals

Venture capitals are professionally managed funds who invest in companies that have huge potential.

e Business incubators & Accelerators



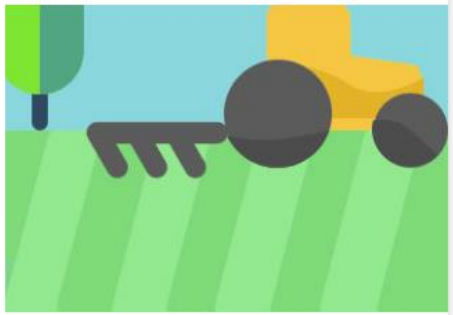
About Approach Our Impact Programs Resources Portfolio Contact Apply for Incubation

Focus Sectors

We have built intelligence and expertise in three main sectors.

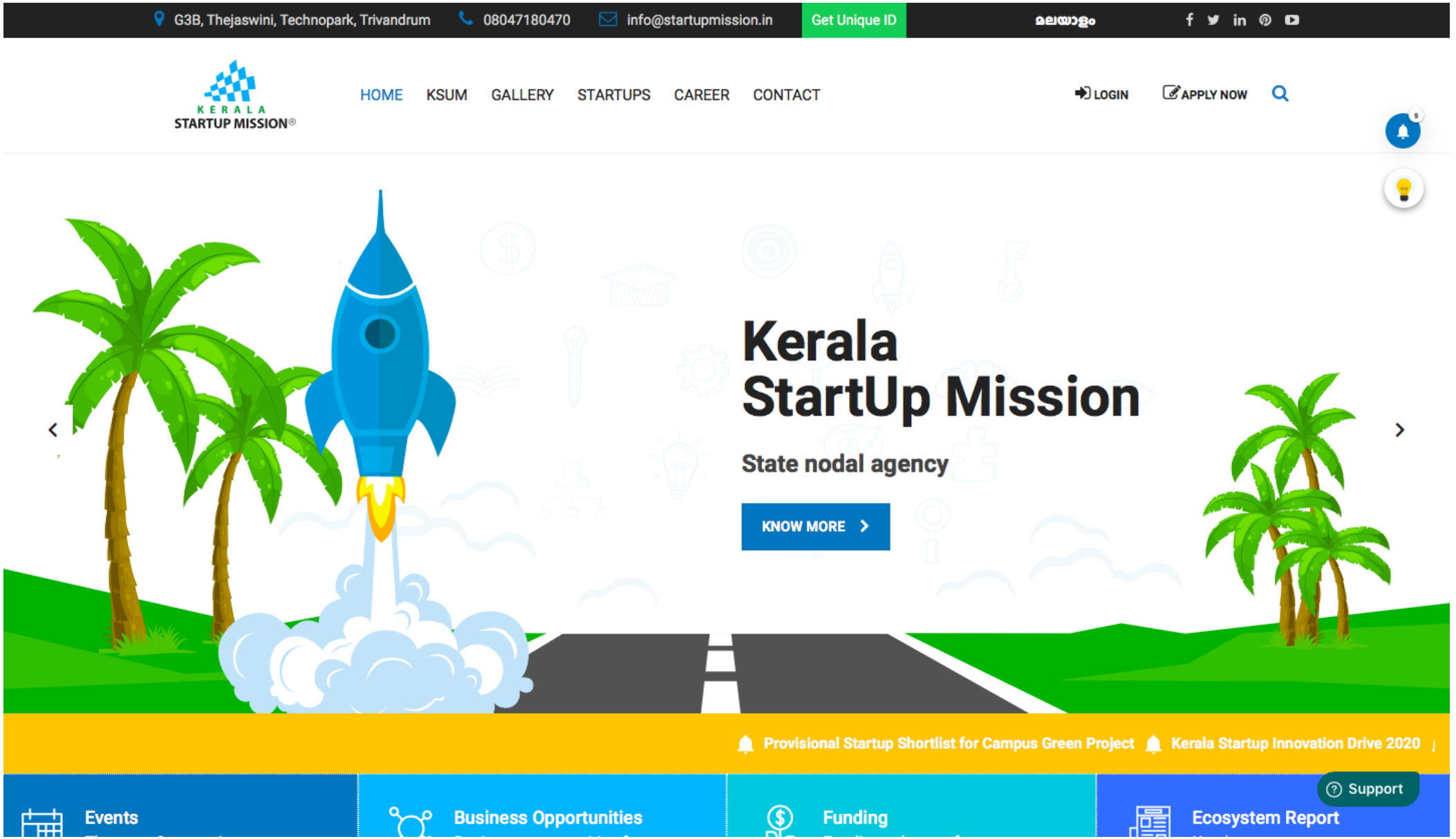
Healthcare

We support invention based social enterprises focused on improving health outcomes for underserved communities



Agriculture

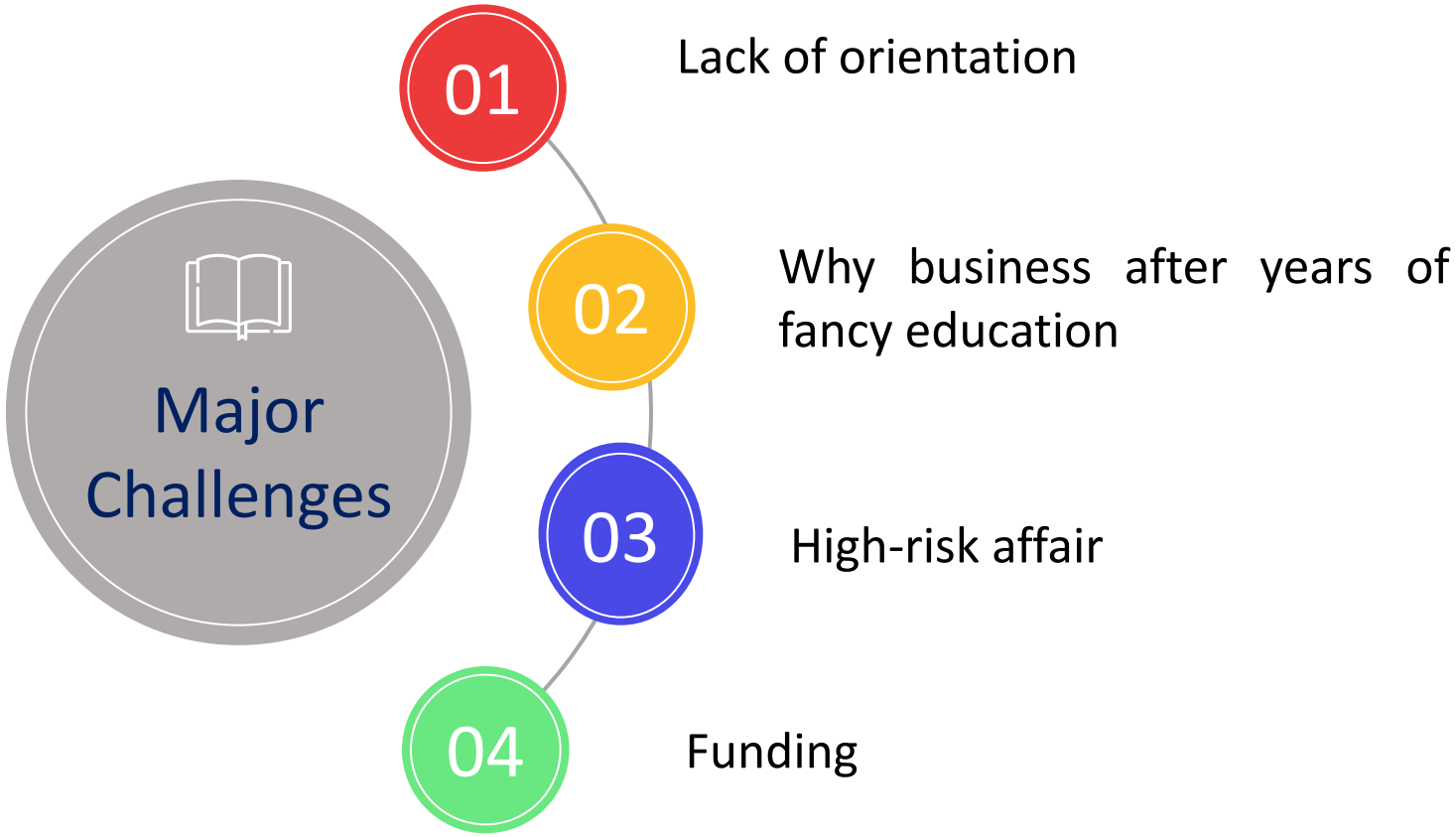
We work with social enterprises focused on improving livelihoods of smallholder farmers, making agriculture more


G3B, Thejaswini, Technopark, Trivandrum
08047180470
info@startupmission.in
Get Unique ID
മലയാളം
KERALA STARTUP MISSION
HOME
KSUM
GALLERY
STARTUPS
CAREER
CONTACT
LOGIN
APPLY NOW
Kerala StartUp Mission
State nodal agency
KNOW MORE
Provisional Startup Shortlist for Campus Green Project
Kerala Startup Innovation Drive 2020
Support
Events
Business Opportunities
Funding
Ecosystem Report

f

Government schemes & Loans

- Mudra loan
- MSME government business loan scheme
- District entrepreneurship development cells



Overcome challenges by better planning

Thank You

MICROBES AND ANTIBIOTICS

by

Sneha susan joshy

pharm d intern

GRAM-ve	GRAM+ve ORGANISMS	ANAEROBIC
Escherichia Haemophilus(B) Klebsiella Meningococcus gonococcus Actinobacillus(B) Aeromonas(B) Brucella Citrobacter Enterobacter Enterobacteriaceae Francisella Legionella Neisseria Pseudomonas Salmonella Shigella Vibrio	Staphylococcus Streptococcus Enterococcus Micrococcus Mycobacterium tuberculosis Clostridium botulinum Corynebacterium diphtheria Clostridium tetani Bacillus anthrax	Actinomyces—GP Bacteroides—GN Clostridium—GP Fusobacterium—GN Lactobacillus—GP GP = Gram-positive GN = Gram negative

COMMON BACTERIA AND INFECTIONS

- RESPIRATORY TRACT INFECTIONS- GRAM+ve(STREPTOCOCCUS,HAEMOPHILUS)
- SKIN IFECTIONS -GRAM -ve (STAPHYLOCOCCAL)
- URINARY TRACT INFECTIONS -GRAM NEGATIVE(ECOLI)

All cocci are +ve except meningo,gono

All bacilli are –ve except DATA(diphteria,actinomyces,tetanus,anthrax)

ANTIMICROBIAL RESISTANCE

unresponsiveness of m.o to an AMA

- MDR(multidrug resistance)

Non susceptibility to atleast one agent in 3/more antimicrobial categories

Bacteria that resist treatment with more than one antibiotic are called MDROs

Eg:MRSA(methicillin resistant staphlococus aureus)

VRSA

- XDR(extensively drug resistance)

Non susceptibility to atleast one agent in all but 2/fewer antimicrobial categories

- ESBLs(extended spectrum beta lactamase producers)

gram negative organisms(enterobacteriacea,klebsilla,ecoli)

Inactivate beta lactum type antibiotics

- NDM- new delhi metallo betalactamse 1

enzyme that make bacteria resistant to broad range of beta lactum antibiotics

Eg: gram negative –ecoli, klebsilla

- CRA(carbapenem resistant Acinetobacter baumani)

Resistant to nearly all antibiotics

- CRE (carbapenem resistant enterobacteriacea)

resistant to an antibiotic class(carbapenems)

Classification of Antibiotics

Based on mode of Action

- Bacteriostatic
- Bactericidal

Based on their spectrum of action

- Broad-spectrum
- Narrow Spectrum

BASED ON MODE OF ACTION

BACTERIOCIDAL(kill)

Inhibition of cellwall synthesis

PENCILLINS,CEPHALOSPORINS,AMINOGLYCOSIDES,VANCOMYCINS,

FLUROQUINOLONES,RIFAMPICIN,METRONIDAZOLES

"P &C Are Very Cidal For Real Microbes"

BACTERIOSTATIC(prevent)

inhibition of protein synthesis

SULFAMETHOXAZOLE,TETRACYCLINES,TRIMETHOPRIM,ERYTHROMYCIN,LINEZOLID

CHLORAMPHENICOL,CLINDAMYCIN

STTEL -CC

BASED ON SPECTRUM

- NARROW SPECTRUM

Lincosamides(lincomycin,clindamycin),Glycopeptides(vancomycins,teicoplainin),Aminoglycosides(strepto,genta,amikacin),macrolides(erythro, clarithro,azithro)

LIGAMent/GLAM

BROAD SPECTRUM

Tetracyclines(doxycycline),cephalosporins, pencillin,chloramphenicol,fluroquinolones(ciprofloxacin,nor) sulphonamides

Antibiotic Classes

Gram Coverage

1. AmiNOglycosides - Gram (-) = NO
2. Cephalosporins - Gram (+)/(-)
3. Tetracyclines - Gram (+)/(-)
4. Penicillins - Gram (+)/(-)
5. Sulfonamides - Gram (+)/(-)
6. Fluoroquinolones - Gram (+)/(-)
7. Macrolides - Gram (+)
8. Carbapenems - Gram (+)/(-)
9. Lincosamides - Gram (+)
10. Glycopeptides - Gram (+)

GLAM

CEPHALOSPORINS

Antimicrobial	First-Generation	Second-Generation	Third-Generation	Fourth-Generation	Fifth-Generation	Cephalosporin/ β-Lactamase Inhibitor
Examples	Cefadroxil (PO) Cefazolin (IV) Cephalexin (PO)	Cefaclor (PO) Cefotetan (IV) Cefoxitin (IV) Cefprozil (PO) Cefuroxime axetil (PO) Cefuroxime sodium (IV)	Cefdinir (PO) Cefditoren (PO) Cefixime (PO) Cefotaxime (IV) Cefpodoxime proxetil (PO) Ceftazidime (IV) Ceftriaxone (IV, IM)	Cefepime (IV)	Ceftaroline (IV)	Ceftazidime/ avibactam (IV) Ceftolozane/tazobactam (IV)
Mechanism of Action	Inhibits cell wall synthesis					β-lactamase inhibitor binds to β-lactamase, prevents it from breaking down cephalosporin Inhibits cell wall synthesis
Spectrum of Activity	**Gram +:** *Staphylococcus* (except MRSA and MRSE), *Streptococcus*	**Gram +:** *Staphylococcus* (coverage not as good as first-generation) and *Streptococcus* (slightly better than first-generation)	**Gram +:** *Staphylococcus* (No MRSA or MRSE) and *Streptococcus*	**Gram +:** *Staphylococcus* (No MRSA or MRSE) and *Streptococcus*	**Gram +:** *Staphylococcus* (including MRSA, MRSE, VRSA) and *Streptococcus*	**Gram +**: *Streptococcus*

(continued)

Antimicrobial	First-Generation	Second-Generation	Third-Generation	Fourth-Generation	Fifth-Generation	Cephalosporin/ β-Lactamase Inhibitor
Spectrum of Activity *(Cont'd)*	**Gram –:** *E. coli, Klebsiella,* and *Proteus mirabilis*	**Gram –:** *E. coli, Klebsiella, Proteus, Neisseria, Moraxella, H. influenzae*	**Gram –:** *E. coli, Klebsiella, Proteus, Neisseria, Moraxella, Haemophilus, Salmonella, Shigella* (Note: Most *Enterobacteriaceae* are covered)	**Gram –:** *Enterobacteriaceae, Moraxella, Haemophilus, Neisseria* Better gram (–) coverage than the third-generation, including *Pseudomonas* and stable against some AmpC-producing β-lactamases	**Gram –:** Similar to third-generation; *Enterobacteriaceae, Haemophilus, Moraxella, Neisseria*	**Gram–**: *E. coli, Klebsiella, Proteus, Enterobacter, Citrobacter, Providencia, Pseudomonas*
	Anaerobes: *Actinomyces Lactobacillus, Peptococcus, Peptostreptococcus, P. acnes*	**Anaerobes:** *Peptococcus, Peptostreptococcus, P. acnes,* cefoxitin and cefotetan have broad anaerobic coverage including *B. fragilis;* however, resistance is increasing	**Anaerobes:** *Peptococcus, Peptostreptococcus, P. acnes,* cefotaxime and cefoperazone have some gram-negative anaerobic activity; however, not *B. fragilis*	**Anaerobes:** No reliable coverage	**Anaerobes:** No reliable coverage	**Anaerobes:** Broad including *B. fragilis* (ceftolozane/ tazobactam only)
	Atypical: None	**Atypical:** None	**Atypical:** None	**Atypical:** None	**Atypical:** None	**Atypical:** None
Spectrum of Activity Summary	Ceftaroline is the only cephalosporin with MRSA activity. No enterococcal activity across the class. In general, as you increase in generation you gain better gram-negative activity. Ceftazidime, cefepime, ceftazidime/avibactam, and ceftolozane/tazobactam cover *Pseudomonas*. Cefoxitin, cefotetan, cefotaxime, and cefoperazone have good anaerobic activity. Ceftazidime/avibactam and ceftolozane/tazobactam have activity against some carbapenemase-producing organisms.					

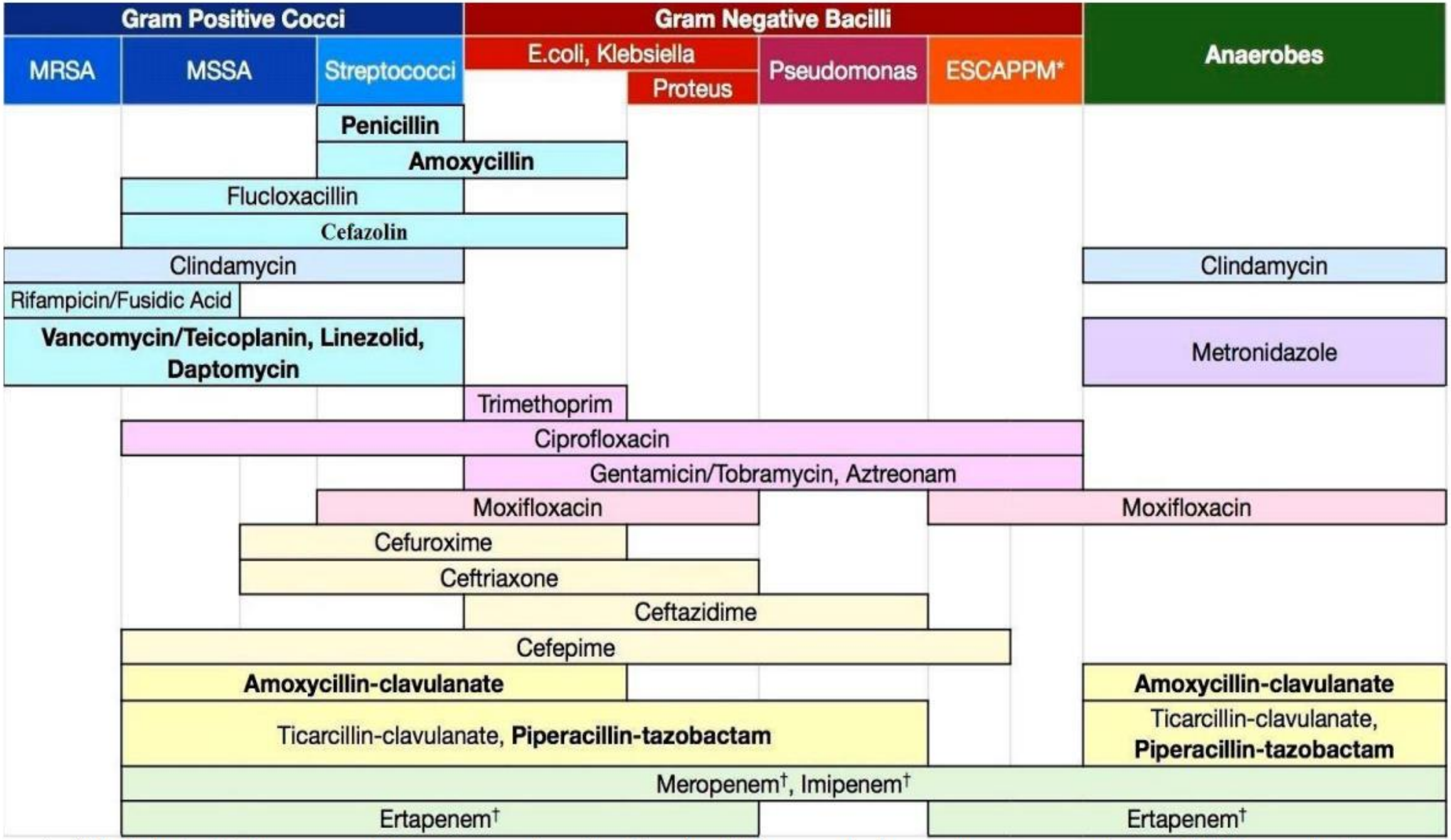
BETA LACTAMASE INHIBITORS

- Beta lactamases are family of enzymes produced by many gram

+ve and gram –ve bacteria that inactivate b-lactam antibiotics by opening b-lactum ring

Beta lactamase inhibitors binds to beta lactamase prevent its from breaking down cephalopsorins inhibits cell wall synthesis

- Clavulanic acid
- Sulbactum
- Tazobactum


Gram Positive Cocci
Gram Negative Bacilli
MRSA
MSSA
Streptococci
E.coli, Klebsiella
Proteus
Pseudomonas
ESCAPPM*
Anaerobes
Penicillin
Amoxycillin
Flucloxacillin
Cefazolin
Clindamycin
Clindamycin
Rifampicin/Fusidic Acid
Vancomycin/Teicoplanin, Linezolid, Daptomycin
Metronidazole
Trimethoprim
Ciprofloxacin
Gentamicin/Tobramycin, Aztreonam
Moxifloxacin
Moxifloxacin
Cefuroxime
Ceftriaxone
Ceftazidime
Cefepime
Amoxycillin-clavulanate
Amoxycillin-clavulanate
Ticarcillin-clavulanate, Piperacillin-tazobactam
Ticarcillin-clavulanate, Piperacillin-tazobactam
Meropenem†, Imipenem†
Ertapenem†
Ertapenem†

Antibiotics for gram +ve	**Antibiotics for gram –ve**	**Anaerobic**
Vancomycin	Ampicillin + sulbactam	metronidazole
Ciprofloxacin	cefazolin	Carbapenems
Chloramphenicol	cefuroxime	Cholramphenicol
Levofloxacin	meropenam	tigecycline.
Gentamicin	ciprofloxacin	Clindamycin
Pencillin	Linezolid	
Clindamycin		

Amoxicillin-clavulanate
Ticarcillin-clavulanate
Piperacillin-tazobactum
Merpenem,imipenem

} *gram +ve,gram –ve, anaerobs*

ciprofloxacin } *gram+ &-ve*

metronidazole } *anaerobic*

ANTIBIOTIC USE

1. Making a clinical diagnosis
2. Limiting empiric antibiotic therapy
3. Know your bugs
4. Choose appropriate antibiotic
5. De escalation/ modification
6. Stop antibiotics in some situations
7. Reduce duration of therapy

RESPIRATORY ANTIBIOTICS PRESCRIBED IN PEDIATRICS

AGE CATEGORY

Age-group	Age
Newborn	0 days to 1 month
Infant	1 month to 1 year
Toddler	1 to 3 years
Preschool	3 to 6 years
School age child	6 to 12 years
Adolescent	12 to 18 years

UPPER RESPIRATORY TRACT INFECTIONS (URTI)

DIAGNOSIS	CAUSATIVE AGENT	FIRST LINE	SECOND LINE /ALTERNATIVE
RHINITIS	Viral -RSV Stre.pneumonia,H. influenza	Self limiting, symptomatic treatment Antimicrobial therapy not needed	
PHARYNGITIS	Viral/bacterial	Amoxicillin	Cephalexin(10 days) Azithromycin(5days)
TONSILITIS	Bacterial	“	“
OTITIS MEDIA	Pneumococci,H.influenza	Amoxicillin(80-90mg/kg/day)	Co-amoxiclav(80-90mgkg/day) Cefuroxime Cefpodoxime Ill patient with vomiting-Ceftriaxone for 3days(50mg/kg/day)
SINUSITIS	Bacterial	Amoxicillin	“
EPIGLOTITIS/LARYNGITIS	H.influenza	Airway, suction,CPAP Ceftriaxone(100mg/kg/day) Cefotaxime)(200mg/kg/day	

LOWER RESPIRATORY TRACT INFECTION(LRTI)

DIAGNOSIS	CAUSATIVE AGENT	FIRST LINE		SECOND LINE
COMMUNITY ACQUIRED PNEUMONIA	Bacterial/Viral	< 3 months	**IV**: always Cefotaxime± Gentamycin/ Amikacin Ceftriaxone	**IV**:Pipracillin-tazobactum ± Gentamycin/ Amikacin Cefoperazone –sulbactum ± Gentamycin/ Amikacin
	Pneumococci,H.influenza	3m -5yrs	**ORAL**: Amoxicillin **IV**: Ampicillin	**ORAL**: Co-amoxiclav/ Cefpodoxime/ Cefuroxime **IV**: Co-amoxiclav/ Cefotaxime/ Ceftriaxone
	Pneumococci,Mycoplasma	> 5yrs	**ORAL**: Amoxicillin **IV**: Ampicillin	**ORAL**: Co-amoxiclav/ Cefpodoxime/ Azithromycin **IV**: Co-amoxiclav/ Cefotaxime/ Ceftriaxone/ Azithromycin
HOSPITAL ACQUIRED PNEUMONIA		Piperacillin+Tazobactum(80mg/10mg/kg/day) Q6hrs Cefoperazone-sulbactum Cefepime Meropenem		

PENCILLINS

- **AMOXICILLIN**

Usual dose: oral- 25-50mg/kg/day in divided doses(bd)

suspecting S.pneumonia-45-90mg/kg/day bd

Brand names: Tab.Mox kid 125mg

Tab.Moxikind CV -500mg

syp.Mox redimix(250/5)

AMOXICILLIN +CLAVULANIC ACID

Usual dose: oral -25-50mg/kg/day in divided doses(bd)

IV -50-100mg/kg/day bd

Brand names: Tab.Advent 625mg(500+125)

tab. Augmentin Duo 625mg

syp Advent forte –(400/5)

syp Augmentin Duo (200/5)

- **AMPICILLIN**

Usual dose : 100mg/kg/day TIDorQID

CEPHALOSPORINS

- **First generation**

p/o: cephalexin -20-50mg/kg/day Q6-Q8hrs

SYP.SPORIDEX 125mg/5ml,250mg/5ml

Max dose:1g

gram +ve,gram -ve

atypical

- **Second generation**

p/o: cefuroxime axetil -30mg/kg/day bd

Cefakind 12mg, 250mg,500mg

Wakcef 500mg

Iv:cefuroxime Na-50- 100mg/kg/day Q8hrs(TID)

staphlyo-coverage

not good as 1st gen

streptoc-slightly

better than 1st gen

- **Third generation**
- **ORAL**

Cefixime

Usual dose**:** oral – 8mg/kg/day bd

syp. Taxim o(50/5ml)

syp. Taxim o forte(100/5ml)

Cefpodoxime

Usual dose : 10mg/kg/day bd

Monocef o(100mg/5ml)

same as 1st gen

more gram –ve coverage

- **IV**

Ceftriaxone -50mg/kg/day bd/tid

Life threatening-100mg/kg/day

Cefotaxime-100mg/kg/day bd/tid

fourth generation

Cefipime(IV):100-10mg/kg/day in 3 divided dose

- **MACROLIDES**

AZITHROMYCIN

Usual dose: 10mg/kg/day OD

Max: 500mg

Brand names: SYP.AZEE 200mg/5ml

FLUROQUINOLONES

LEVOFLOXACIN

Usual dose: 10-15mg/kg/day in 2 divided doses PO/IV

AMINOGLYCOSIDES

Amikacin- < 3months-15 mg/kg/d, OD

3m-5yrs-100 mg/ kg/d, TID or QID

gentamicin :5–7 mg/kg/d, OD

A case on LRTI

- A 10 yr 29.2kg weighed male patient got admitted in pediatrics with chief complaints of fever,cough*3days and vomiting and lab report shows TC and crp was elevated and diagnosed as wheeze associated LRTI

Ip medications

Inj. Cefuroxime 750mg IV tds *5 days

Inj.ondansetron 5mg stat

Syp.Ascoril LS 5ml tds

Tab. Azithromycin OD*2 days

DISCHARGE MEDICATIONS

- Tab.Azithromycin ?
- Syp. Ascoril LS 5ml TDS
- Syp. Mefthal sos

CALCULATION


Thank
You

MANAGEMENT OF COMPLICATIONS ASSOCIATED WITH CKD

Simi Grace Joseph

Pharm d intern

What is CKD ?

- Kidney damage for more than 3 months, as defined by structural or functional abnormalities of the kidneys manifest by either

1. Pathological abnormalities (glomerulosclerosis , tubulointerstial fibrosis)
2. Markers of kidney damage (abnormalities in urine or blood, imaging tests)

Complications associated with CKD

- The main complications associated with CKD are

1. Fluid and electrolyte abnormalities
2. Metabolic acidosis
3. Anaemia of chronic kidney disease
4. Secondary hyperparathyroidism and renal osteodystrophy
5. Cardiovascular disease

ELECTROLYTE ABNORMALITIES DUE TO KIDNEY DISEASE

- Maintenance of fluid volume, osmolarity, electrolyte balance, and acid–base status are all regulated in large part by the kidney, and their homeostasis is altered in patients with impaired kidney function.
- Blood vol and plasma osmolality are regulated by serum sodium and water balance.
- Impaired kidney functions can alter the regulation of serum sodium levels and water balance leading to consequences related to its imbalance.
- The electrolytes are monitored to understand the patient status, disease condition and progress of disease.

Sodium and water balance

- Sodium and its accompanying anions, chloride and bicarbonate, makes up 90 % of total osmolality of ECF, whereas intracellular osmolality is primarily dependent on the concentration of potassium and its accompanying anions.
- Hypo- and hypernatremia are syndromes of altered plasma tonicity and cell volume.
- Hyponatermia (Na <13mEq/L)is predominantly the result of an excess of extracellular water relative to sodium because of impaired water excretion.
- Hypernatermia (Na >135mEq/L) is always associated with hypertonicity and results from a deficit of water relative to ECF sodium content.

- Patients with chronic, mild hyponatremia (serum sodium concentration greater than 125 to130 mEq/L) are usually asymptomatic.
- Patients with moderate (115 to 125 mEq/L) to severe (<110 to 115 mEq/L) or rapidly developing hypotonic hyponatremia often present with a range of neurologic symptoms resulting from hypoosmolality-induced volume expansion of brain cells.
- Classic symptoms include nausea and malaise, headache, lethargy, restlessness, and disorientation, and in some seizures, coma, permanent brain damage, respiratory arrest, brainstem herniation, and death.

Treatment

- It is important for both the short- and long-term management of the patient to treat the underlying cause of hyponatremia.
- Patients with moderate to severe hyponatermia requires rapid Na correction.
- Hypovolemic hypotonic hyponatremia is usually best accomplished with 0.9% sodium chloride solution as these patients have both sodium and water deficits, and 100% of the water stays in the ECF compartment.

- Active correction of euvolemic and hypervolemic hypotonic hyponatremia in patients who do not require rapid correction is usually best accomplished by water restriction.
- Demeclocycline, vasopressin V2 receptor antagonists, or sodium chloride plus a loop diuretic, can be used if the initial response is not adequate.
- In patients with severe symptoms, 3% sodium chloride solution (possibly combined with furosemide) should initially be used to more rapidly correct the hyponatremia.
- Long term management of sodium correction may be required in some patients and can be achieved by water restriction, increasing sodium intake, and/or the use of an AVP antagonist.

Hyperkalemia

- Hyperkalemia, defined as a serum potassium concentration greater than 5.5 mEq/L, can be further classified according to its severity: mild hyperkalemia (serum potassium 5.5 to 6 mEq/L), moderate hyperkalemia (6.1 to 6.9 mEq/L), and severe hyperkalemia (>7 mEq/L).
- Severe hyperkalemia occurs more commonly in elderly patients with renal insufficiency who receive chronic oral potassium supplementation.
- The kidneys excrete 80% of the daily potassium intake. Therefore when the kidney is unable to excrete potassium appropriately, as in acute renal failure (ARF) and stage 4 to 5 CKD, potassium is retained and often results in hyperkalemia.

Treatment

- The goals of therapy for the treatment of hyperkalemia are to antagonize adverse cardiac effects, reverse any symptoms that are present, and return the serum and total body stores of potassium to normal
- There is often a delay between diagnosis of hyperkalemia and institution of dialysis, which necessitates the use of other temporizing measures, such as IV calcium gluconate, insulin and glucose, nebulized β2-adrenergic agonists (albuterol), and sodium polystyrene sulfonate
- Unfortunately, shifting potassium into the intracellular fluid compartment with insulin and glucose or with albuterol makes removal of potassium via dialysis more difficult.
- Multiple dialysis sessions may be necessary following potassium redistribution to the extracellular space.

- Sodium polystyrene sulfonate (with sorbitol), a potassium–sodium exchange resin, can be given orally in doses of 25 to 50 g to increase potassium excretion via the ileum and colon.
- Sodium bicarbonate therapy is no longer advocated in the treatment of ESRD hyperkalemia unless severe metabolic acidosis is also present, because the potassium lowering effect is unreliable.
- Loop diuretics, a standard pharmacologic treatment option for hyperkalemia, are ineffective in patients with ESRD

ANEMIA OF CHRONIC KIDNEY DISEASE

- When your kidneys are damaged they produce less erythropoietin.
- If the Hb is less than 12 g/dL in adult females or less than 13.5 g/dL in adult males, a complete workup for anemia of CKD should be done.

- This includes evaluation of other causes of anemia such as bleeding, deficiencies in vitamin B12 or folate, or other disease states that contribute to anemia, including human immunodeficiency virus infection and malignancies.
- As the primary cause of resistance to therapy for anemia of CKD, iron status must be evaluated.

- Iron deficiency manifests as a microcytic anemia and is accompanied by a low mean corpuscular volume, whereas deficiencies in vitamin B12 and folate present as a macrocytic anemia with an increase in mean corpuscular volume.

- Iron indices that should be monitored include the TSat, an indicator of iron immediately available for delivery to the bone marrow, and serum ferritin, an indirect measure of storage iron. Transferrin is the carrier protein for iron and, as a protein, may be affected by nutritional status.
- The TSat is calculated as ([serum iron/TIBC] × 100), where TIBC is the total iron-binding capacity.

- If the TSat and serum ferritin values are below the desired threshold iron supplementation is warranted prior to starting ESA therapy. If all other causes of anemia are ruled out and the anemia persists despite iron supplementation, patients should be treated with either epoetin alfa or darbepoetin alfa.

TREATMENT

- The desired outcomes of anemia management are to increase oxygen-carrying capacity, thereby decreasing dyspnea, orthopnea, and fatigue, and to prevent long-term consequences such as LVH and cardiovascular mortality.

- To achieve these goals one must have adequate iron, folate, and B12, and sufficient levels of ESAs. Other factors that contribute to worsening of anemia, such as blood loss and other causes of resistance to ESA therapy, should also be identified and corrected if possible

TABLE 47-2 Target Parameters for Anemia Management in Chronic Kidney Disease

Parameter	Stage 4 CKD and Peritoneal Dialysis Patients	Hemodialysis Patients
Hb	11–12 g/dL	11–12 g/dL
TSat[a]	>20%	>20%
CHr	–	>29 pg/cell
Serum ferritin[a]	>100 ng/mL	>200 ng/mL

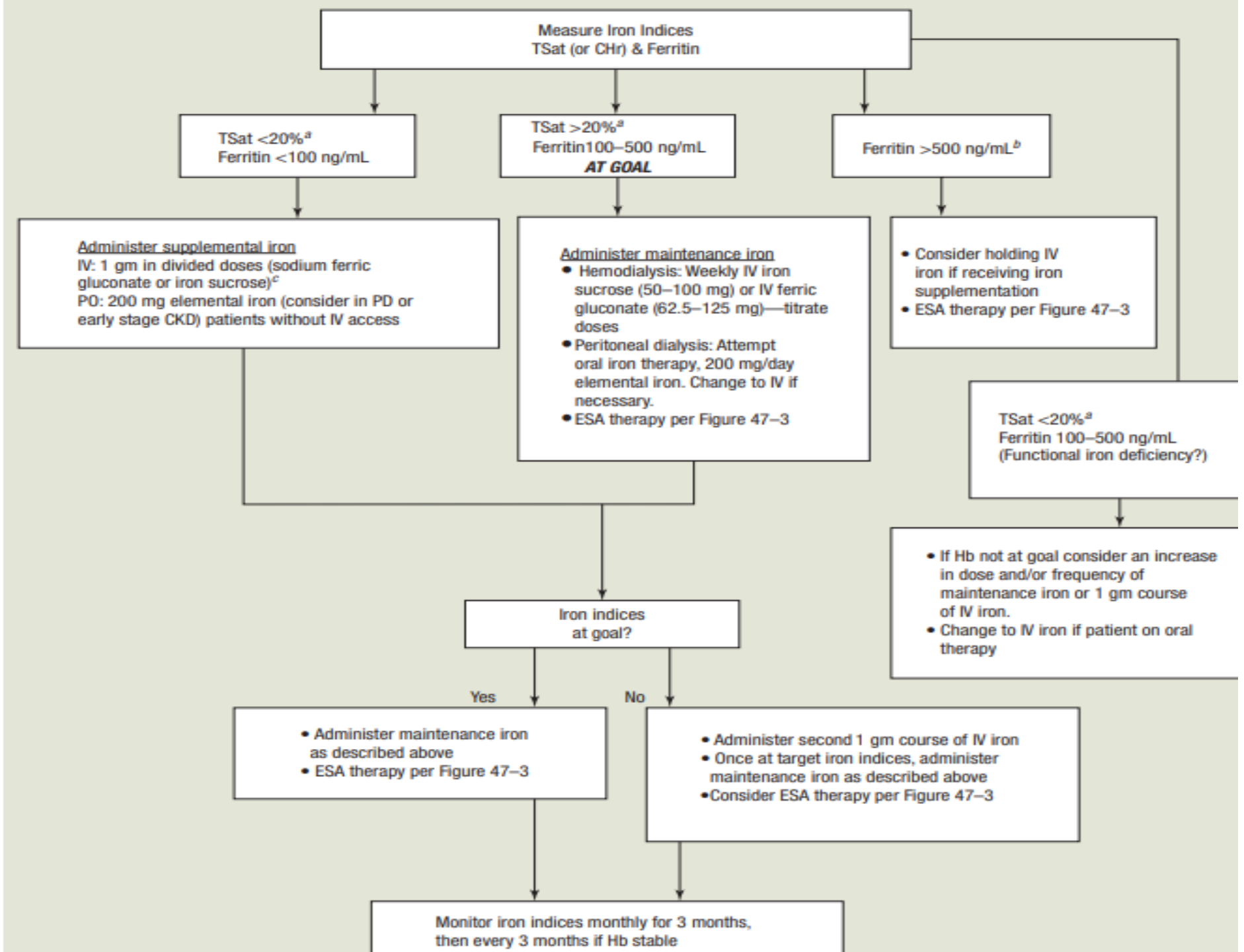
Pharmacologic Therapy

- Pharmacologic therapy for anemia of CKD includes chronic therapy with an ESA to correct erythropoietin deficiency and iron supplementation to correct and prevent iron deficiency caused by ongoing blood loss and increased iron demands associated with the initiation of erythropoietic therapy.

- Iron therapy is first-line therapy for anemia of CKD if iron deficiency is diagnosed, and for some patients the target Hb may be achieved without concomitant ESA therapy.

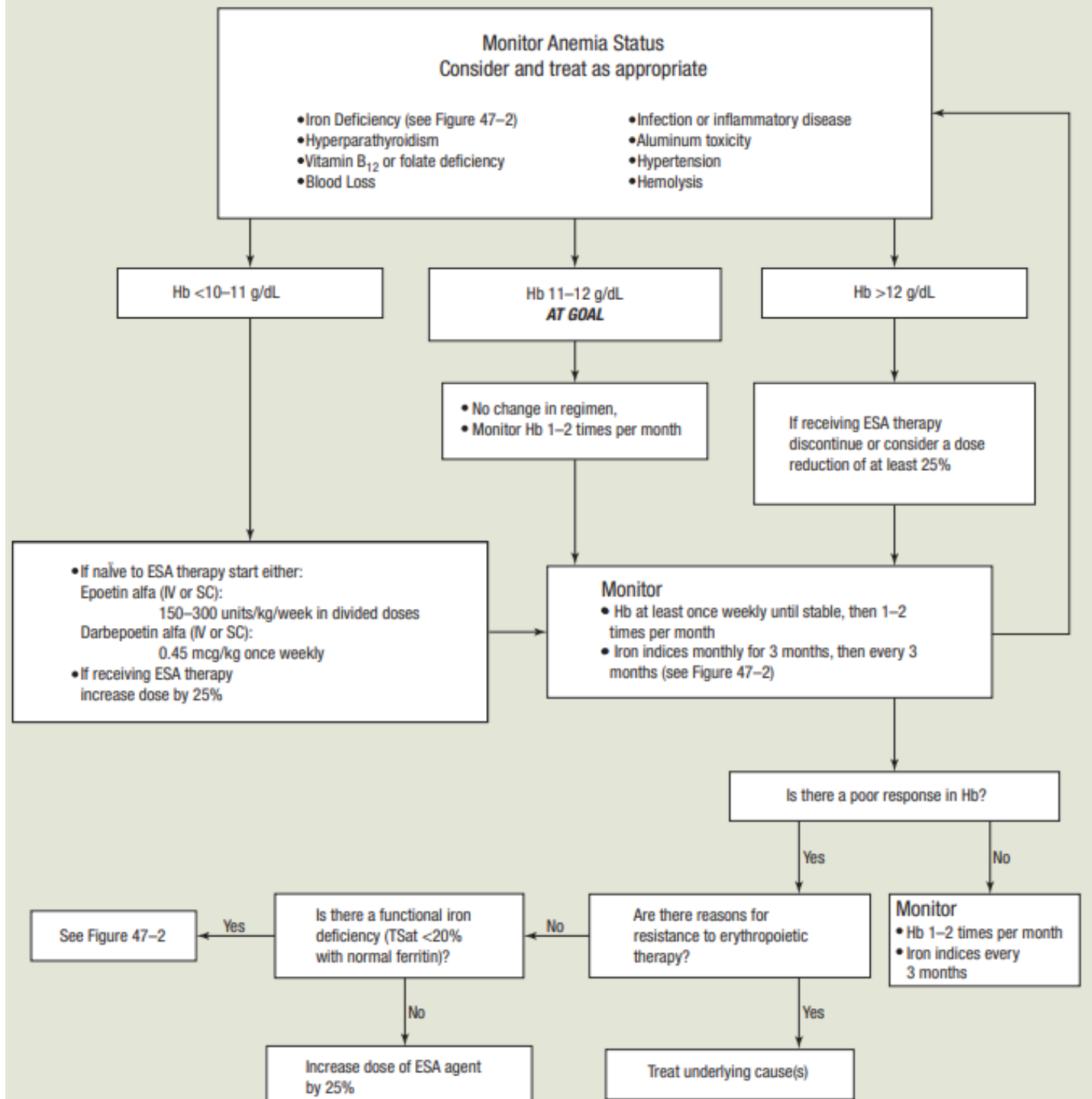
Iron Supplementation

- If TSat (or content of hemoglobin in the reticulocytes) and serum ferritin are below goal indices, iron supplementation is recommended. Options for iron supplementation include oral and IV therapy.
- Available oral iron preparations differ in their content of elemental iron. Products available for oral therapy include ferrous salts (ferrous sulfate, ferrous fumarate, and ferrous gluconate), polysaccharide iron complex, and, most recently, a heme iron polypeptide formulation.
- Four IV iron products are currently available : two composed of iron dextran, sodium ferric gluconate, and iron sucrose


Measure Iron Indices
TSat (or CHr) & Ferritin
TSat <20%[a]
Ferritin <100 ng/mL
TSat >20%[a]
Ferritin100–500 ng/mL
AT GOAL
Ferritin >500 ng/mL[b]
Administer supplemental iron
IV: 1 gm in divided doses (sodium ferric gluconate or iron sucrose)[c]
PO: 200 mg elemental iron (consider in PD or early stage CKD) patients without IV access
Administer maintenance iron
• Hemodialysis: Weekly IV iron sucrose (50–100 mg) or IV ferric gluconate (62.5–125 mg)—titrate doses
• Peritoneal dialysis: Attempt oral iron therapy, 200 mg/day elemental iron. Change to IV if necessary.
• ESA therapy per Figure 47–3
• Consider holding IV iron if receiving iron supplementation
• ESA therapy per Figure 47–3
TSat <20%[a]
Ferritin 100–500 ng/mL
(Functional iron deficiency?)
• If Hb not at goal consider an increase in dose and/or frequency of maintenance iron or 1 gm course of IV iron.
• Change to IV iron if patient on oral therapy
Iron indices at goal?
Yes
No
• Administer maintenance iron as described above
• ESA therapy per Figure 47–3
• Administer second 1 gm course of IV iron
• Once at target iron indices, administer maintenance iron as described above
•Consider ESA therapy per Figure 47–3
Monitor iron indices monthly for 3 months, then every 3 months if Hb stable

Erythropoietic-Stimulating Agent Therapy

- ESAs are required to stimulate differentiation of erythroid progenitor stem cells and induce the release of reticulocytes from the bone marrow to the bloodstream where they mature into erythrocytes (red blood cells).
- Available ESAs include epoetin alfa and darbepoetin alfa. These agents are glycoproteins manufactured by recombinant DNA technology that have the same biologic activity as endogenous erythropoietin. Although the amino acid sequence of epoetin alfa is identical to the endogenous protein, the carbohydrate structure differs.


Monitor Anemia Status
Consider and treat as appropriate
•Iron Deficiency (see Figure 47–2)
•Hyperparathyroidism
•Vitamin B_{12} or folate deficiency
•Blood Loss
•Infection or inflammatory disease
•Aluminum toxicity
•Hypertension
•Hemolysis
Hb <10–11 g/dL
Hb 11–12 g/dL
AT GOAL
Hb >12 g/dL
• No change in regimen,
• Monitor Hb 1–2 times per month
If receiving ESA therapy discontinue or consider a dose reduction of at least 25%
• If naïve to ESA therapy start either:
Epoetin alfa (IV or SC):
150–300 units/kg/week in divided doses
Darbepoetin alfa (IV or SC):
0.45 mcg/kg once weekly
• If receiving ESA therapy
increase dose by 25%
Monitor
• Hb at least once weekly until stable, then 1–2 times per month
• Iron indices monthly for 3 months, then every 3 months (see Figure 47–2)
Is there a poor response in Hb?
Yes
No
Monitor
• Hb 1–2 times per month
• Iron indices every 3 months
Are there reasons for resistance to erythropoietic therapy?
No
Is there a functional iron deficiency (TSat <20% with normal ferritin)?
Yes
See Figure 47–2
Yes
Treat underlying cause(s)
No
Increase dose of ESA agent by 25%

METABOLIC ACIDOSIS

- Individuals with normal kidney function generate enough hydrogen ion to reclaim all filtered bicarbonate and to secrete approximately 1 mEq/kg per day of hydrogen ions, which are generated from the metabolism of dietary proteins.

- As a result, they maintain a constant body fluid pH through the buffering of hydrogen ion by proteins, hemoglobin, phosphate, and bicarbonate. Renal ammoniagenesis and phosphate excretion buffer the urine and facilitate acid excretion.

- In severe CKD, all filtered bicarbonate is reclaimed, but the ability of the kidneys to synthesize ammonia is impaired.

- This decrease in urinary buffer results in decreased net acid excretion and continuous positive hydrogen ion balance; consequently, metabolic acidosis develops.

- A clinically significant metabolic acidosis is commonly seen when the GFR drops below 20 to 30 mL/min (stage 4 CKD). In these patients, the plasma bicarbonate concentration tends to stabilize at 15 to 20 mEq/L

Treatment

- The goals of therapy for patients with CKD are to normalize the pH of the blood (pH of approximately 7.35 to 7.45) and maintain the serum bicarbonate within the normal range (22 to 26 mEq/L).
- In patients on hemodialysis, the goal of therapy is to maintain a predialysis or stabilized bicarbonate concentration at or above 22 mEq/L.

- The replacement dose of alkali (base) needed to restore the serum bicarbonate concentration to normal (24 mEq/L) can be approximated by **multiplying the volume of distribution of bicarbonate (0.5 L/kg) by the patient's body weight (in kilograms) and the patient's base deficit (difference between the patient's serum bicarbonate value and the normal value of 24 mEq/L).**
- The calculated amount of bicarbonate replacement therapy (in milliequivalents) should be administered over several days to prevent volume overload from excessive sodium intake.
- After the serum bicarbonate has normalized, a maintenance regimen of bicarbonate to neutralize daily acid production may be all that is necessary (12 to 20 mEq/day in divided doses).

- Patients with severe acidosis (serum bicarbonate <8 mEq/L; pH <7.2) may require IV therapy .
- The use of alkalinizing salts, such as sodium bicarbonate or citrate/citric acid preparations, is useful to replenish depleted body bicarbonate stores.
- Sodium bicarbonate tablets are manufactured in 325- and 650-mg strengths

SECONDARY HYPERPARATHYROIDISM AND RENAL OSTEODYSTROPHY

- Calcium and phosphorus balance is mediated through the complex interplay of hormones and their effects on bone, the GI tract, kidney, and parathyroid gland.

- What begins as relatively minor imbalances in phosphorus and calcium homeostasis leads to secondary hyperparathyroidism (sHPT) in the short-term and ultimately renal osteodystrophy (ROD) if these metabolic abnormalities are not corrected

- As kidney function declines there is a decrease in phosphorus elimination, which results in hyperphosphatemia and when severe a reciprocal decrease in serum calcium concentration.

- Hypocalcemia is the primary stimulus for release of PTH by the parathyroid glands, the effects of which are mediated by the interaction of ionized calcium with the calcium-sensing receptor on the chief cells of the parathyroid gland

- Hyperphosphatemia also increases PTH synthesis and release through its direct effects on the parathyroid gland and production of prepro-PTH messenger RNA.

- In an attempt to normalize ionized calcium, PTH decreases phosphorus reabsorption and increases calcium reabsorption by the proximal tubules of the kidney (at least until the GFR falls to less than approximately 30 mL/min), and also increases calcium mobilization from bone.

- The result is a correction in calcium and phosphorus, at least in the early stages of CKD; however, this occurs at the expense of an elevated PTH (“the trade-off hypothesis”).

- The increase in PTH is most notable when GFR is less than 60 mL/min per 1.73 m2 (stage 3 CKD) and worsens as kidney function further declines.

- Active vitamin D (1,25-dihydroxyvitamin D3 or calcitriol) promotes increased intestinal absorption of calcium, which helps to normalize ionized calcium.
- Calcitriol also works directly on the parathyroid gland to suppress PTH production.
- The enzyme 1α-hydroxylase is responsible for the final hydroxylation and conversion of the vitamin D precursor, 25-hydroxyvitamin D, to the active form in the kidney.
- As kidney disease progresses this conversion is impaired and vitamin D deficiency results. Calcitriol levels decrease significantly before there is a perceptible rise in PTH in CKD patients.

Nonpharmacologic Therapy

Dietary Phosphorus Restriction

- Dietary phosphorus restriction should be a first-line intervention for management of hyperphosphatemia in patients with CKD and should be initiated for most patients with stage 3, 4, or 5 CKD.
- The K/DOQI guidelines recommend phosphorus restriction to 800 to 1,000 mg/day when the upper levels of phosphorus are reached. This recommendation also holds true for patients with iPTH levels above the recommended range, given the evidence that lowering phosphorus ingestion directly decreases PTH synthesis and secretion.
- The challenge with dietary restriction of phosphorus is providing enough protein to prevent malnutrition, a common problem in the CKD population, because foods high in phosphorus are generally high in protein.
- Examples of foods or beverages that contain high amounts of phosphorus include meats, dairy products, dried beans, nuts, colas, peanut butter, and beer. Nutritional goals must be evaluated on an individual basis

Parathyroidectomy

- Parathyroidectomy is the last therapeutic option for patients with sHPT.

- The K/DOQI guidelines for bone metabolism and disease recommend surgery only for those patients with persistently elevated iPTH (iPTH >800 pg/mL) associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy.

- Surgical approaches include either subtotal parathyroidectomy or total parathyroidectomy with auto transplantation of parathyroid tissue to an accessible site, such as the forearm. P

Pharmacological therapy

- As kidney function declines, dietary restriction of phosphorus alone is usually inadequate to control serum phosphorus.
- Phosphate binding agents are necessary, along with vitamin D therapy and/or calcimimetic therapy, to prevent sHPT

Minimising phosphate absorption: reducing intestinal absorption (phosphate binders)

- Phosphate binders work by binding dietary phosphate and forming insoluble complexes that are excreted by the gut.

a. Calcium-based phosphate binders (calcium carbonate and calcium acetate).

b. Non-absorbable polymers (sevelamer).

c. Heavy metal salts (lanthanum carbonate and aluminium hydroxide).

Calcium-based phosphate binders

- Calcium-based phosphate binders are the most widely prescribed phosphate binders. These are prescribes in cases where both hypocalcemia and hyperphosphatemia occurs.
- The total calcium of serum is distributed as free calcium, calcium bound to proteins and calcium bound to inorganic anions
- About half of the calcium in serum is bound to serum protiens especially albumin
- Changes in albumin concentration cause changes in changes in total calcium.
- In CKD patients there is reduced synthesis and increased degradation of albumin.
- Thus, low serum calcium (hypocalcemia) may be due hypoalbunimia
- So corrected calcium should be calculated
- Corrected calcium (mg/dl) = total calcium + 0.8 (4 – measured albumin mg/dl)

- Calcium carbonate and calcium acetate are the primary preparations used; calcium citrate is also available, but is not recommended since the citrate component increases aluminium absorption.
- Calcium acetate binds approximately twice as much phosphorus as calcium carbonate at comparable doses of elemental calcium. Increased binding potency limits GI calcium absorption; however, calcium acetate is more soluble, and therefore better absorbed than calcium carbonate in an alkaline pH

- The drugs used are calcium carbonate and calcium acetate.

Calcium carbonate : dose stage 3to 5 – not to exceed 2000mg/day

stage 5 – not to exceed 1500mg/day

Calcium acetate : initial 2 capsules of 667mg calcium acetate with each meal

Non-absorbable polymers (sevelamer)

- It is a non-absorbable, synthetic ion-exchange polymer that binds phosphate and inhibits its absorption by the body .Polymers are considered to be as effective as the calcium-based phosphate binders .

- Sevelamer also significantly lowers LDL cholesterol and increases HDL by a mean of 30% and 18%,respectively. This is an added beneficial effect in a population at risk for cardiovascular events.

- The possibility of hypercalcaemia and lowered concentrations of PTH are less likely to occur with sevelamer

- Sevlamer dose

  Serum P 5. 5 – 7. 5 :0.8 g orally 3 times daily

  Serum P greater than or equal to 7. 5 : orally 3 times a day 1.6 g

Heavy metal salts

Lanthanum carbonate (LC)

- Lanthanum carbonate is a phosphate binder recently approved for patients with ESRD.
- Short-term (6 to 28 weeks) and long-term (2 to 3 years) therapy with lanthanum has demonstrated efficacy in controlling phosphorus and maintaining PTH in the target range with less risk of hypercalcemia than calcium-containing binders.
- Initial daily doses are in the range of 750 to 1,500 mg (administered in divided doses with meals) with doses of 1,500 to 3,000 mg often being required to maintain target phosphorus in ESRD patients.
- The poor GI absorption, which limits systemic effects, and high binding capacity with phosphorus makes this an attractive phosphate-binding agent, particularly when options other than calcium-containing binders are needed. Lanthanum is available as a chewable tablet, which may be appealing for some patients.

Vitamin D Therapy

- Vitamin D compounds include ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) that must be converted to the active form in the kidney.

- Calcitriol (1,25-dihydroxyvitamin D3) is the most active form of vitamin D and is available as an oral formulation as well as an IV formulation.

- The currently available vitamin D analogues include paricalcitol and doxercalciferol.

- Calcitriol or one of the vitamin D analogues is required for patients with severe kidney disease because these agents do not require conversion by the kidney to the biologically active form.

Calcimimetics

- Cinacalcet hydrochloride (Sensipar) is a calcimimetic agent approved for treatment of sHPT in ESRD patients and for treatment of hypercalcemia in patients with parathyroid carcinoma.
- Cinacalcet is the first agent in this class to receive FDA approval. This compound acts on the calcium-sensing receptor on the surface of the chief cell of the parathyroid gland to mimic the effect of extracellular ionized calcium and increase the sensitivity of the calcium-sensing receptor to calcium, subsequently reducing PTH secretion.
- The recommended starting oral dose of cinacalcet is 30 mg once daily. The dose should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve the desired PTH levels and to maintain near-normal serum calcium concentrations.

CARDIOVASCULAR DISEASE

- Patients with CKD are at increased risk of cardiovascular disease, independent of the etiology of their kidney disease. Although a clearly unique pathogenesis of cardiovascular disease specific to CKD has not been identified, it is known that manifestations of kidney disease are contributory.
- In addition to traditional cardiac risk factors such as hypertension and hyperlipidemia, diabetes, tobacco use, and physical inactivity, patients with kidney disease have other unique risk factors.
- Among these are elevated levels of C-reactive protein, increased oxidant stress, and hemodynamic overload. Complications such as anemia and metabolic disorders (i.e., abnormalities in Ca, P, and PTH) of CKD are also contributory.
- In particular, arterial vascular disease (e.g., atherosclerosis) and cardiomyopathy are the primary types of cardiovascular disorders present in the CKD population. These disorders lead to development of ischemic heart disease and its manifestations including myocardial infarction.

Hypertension

- As a primary cause or consequence of progressive loss of kidney function, hypertension is prevalent in the majority of patients with CKD
- The pathogenesis of hypertension in CKD is multifactorial, but in many hypertensive dialysis patients, fluid retention is a major contributor.
- In addition to the general pathophysiologic mechanisms responsible for the development of hypertension, patients with ESRD may also have increased sympathetic activity, decreased activity of vasodilators such as nitric oxide, elevated levels of endothelin-1, chronic use of an ESA such as epoetin alfa, hyperparathyroidism, and structural changes in the arteries (e.g., metastatic calcification) as contributing factors.

Treatment

- Most patients with hypertension and CKD require drug regimens that include three or more antihypertensive agents to achieve target blood pressure

- Diuretic therapy is beneficial for management of blood pressure in patients with early CKD; however, thiazide diuretics are not generally effective in patients.

- ACEIs or angiotensin receptor blockers are the preferred agents for patients with progressive CKD and proteinuria. They are also preferred in patients with ESRD because of their potential benefits, including regression of LVH, reduction in sympathetic nerve activity and pulse-wave velocity, improvement in endothelial function, and reduced oxidative stress

- Calcium channel blockers that selectively lower systemic vascular resistance also appear to be effective in the treatment of hypertension in patients with ESRD and are associated with decreased total and cardiovascular mortality

- β-Blockers may be particularly useful in hypertensive CKD patients given the beneficial effects after myocardial infarction.

- In the ESRD population, agents that act on the sympathetic nervous system, such as prazosin, terazosin, doxazosin, clonidine, guanabenz, and guanfacine, may be required in patients who are unresponsive to ACEIs, calcium channel blockers, or β-blocker therapy, and used in conjunction with adequate dialysis

Hyperlipidemia

- CKD with or without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism. It is well established that dyslipidemias cause atherosclerotic cardiovascular disease and there are many compelling reasons to aggressively treat these disorders.
- A clear association between hypercholesterolemia, hypertriglyceridemia, or other lipoprotein changes in patients with CKD and the high incidence of cardiovascular disease has not been demonstrated .

- Drug classes that may prove useful in treatment of lipid disorders include: 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins); the bile acid sequestrants; nicotinic acid; and fibric acids (gemfibrozil and clofibrate).

- Statins are the most effective drugs for lowering LDL and total cholesterol in patients with kidney disease (with or without nephrotic syndrome) and generally should be regarded as the drugs of first choice.

- Drug therapy for hypertriglyceridemia includes a fibrate or nicotinic acid; in general, fibrates are better tolerated.

GINA GUIDELINES

APPLICATION IN PEDIATRIC POPULATION

ALEENA MANOJ
PHARM D INTERN


WHEEZING
COUGHING
SHORTNESS OF BREATH
TIGHTNESS IN THE CHEST
ASTHMA SYMPTOMS


POTENTIAL CHILDHOOD
ASTHMA TRIGGERS:
Weather changes or cold air
Physical activity
Exposure to air pollutants, such as tobacco smoke
Allergies to dust mites, pet dander, pollen or mold
Viral infections such as the common cold
PORTLAND Pediatric GROUP

PHENOTYPES

- Allergic asthma
- Non – allergic asthma
- Adult onset asthma
- Asthma with persistent airflow limitation
- Asthma with obesity

DIAGNOSIS

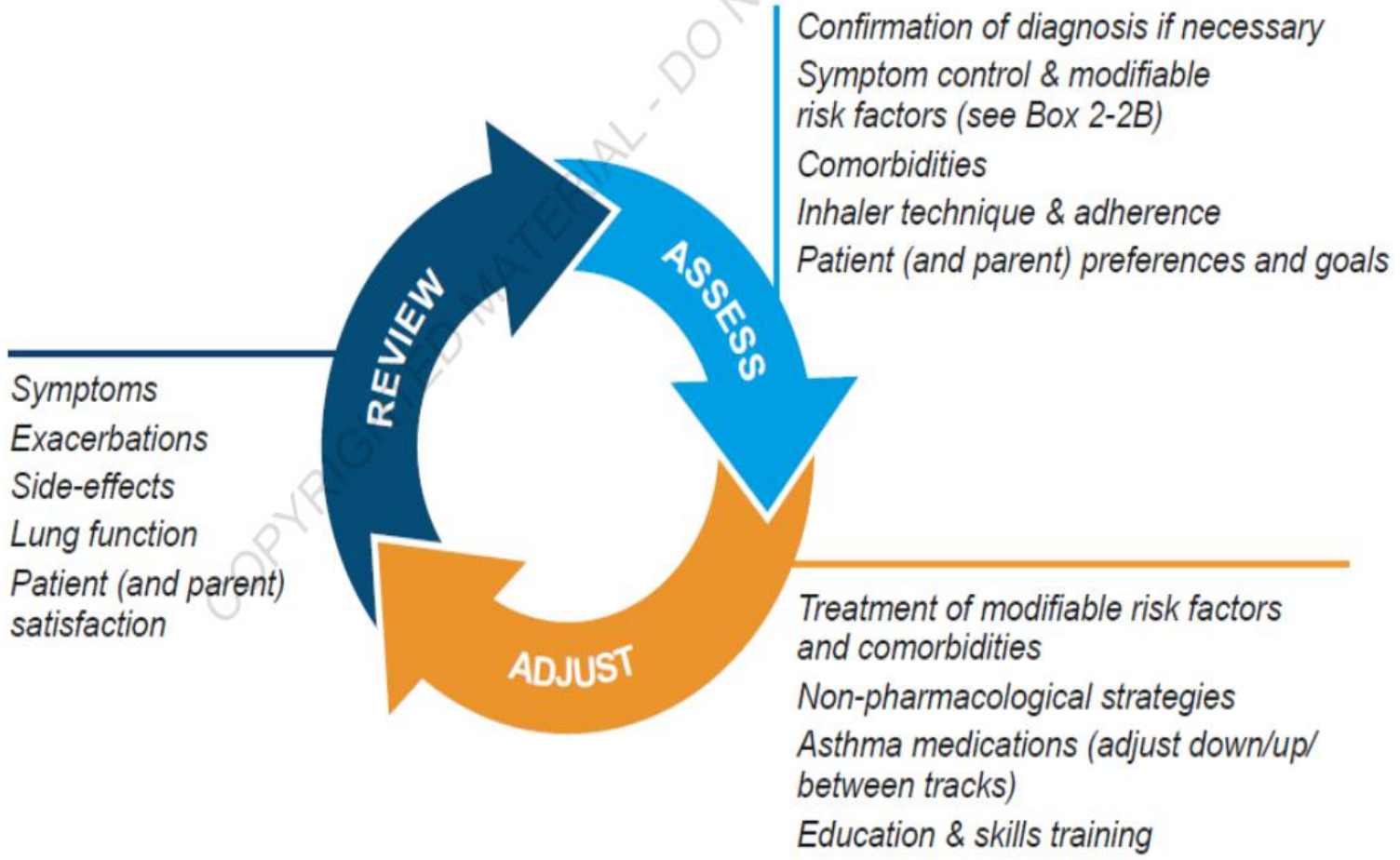
- History of respiratory symptoms
- Confirmed expiratory airflow limitation
- Physical examination
- Bronchial provocation test
- Allergy test
- Exhaled nitric oxide

MANAGEMENT OF ASTHMA

Goals of management

- To achieve good control of symptoms
- To minimize the future risks

The asthma management cycle for personalized asthma care



MEDICATIONS AND STRATEGIES

- Controller medication :-
  - contain ICS
  - used to reduce airway inflammation, control symptoms, and reduce future risks
- Reliever medications:-
  - Provide relief to breakthrough symptoms.
  - For short-term prevention of exercise-induced bronchoconstriction (EIB).
  - Relievers :- low dose ICS- formoterol or SABA.
- Add on therapy
  - LAMA :- TIOTROPIUM BROMIDE
  - ANTI Ig E :- OMALIZUMAB
  - ANTI IL-5 AND ANTI IL5R :- MEPOLIZUMAB & BENRALIZUMAB
  - ANTI IL 4R :- DUPILUMAB

Initial controller treatment

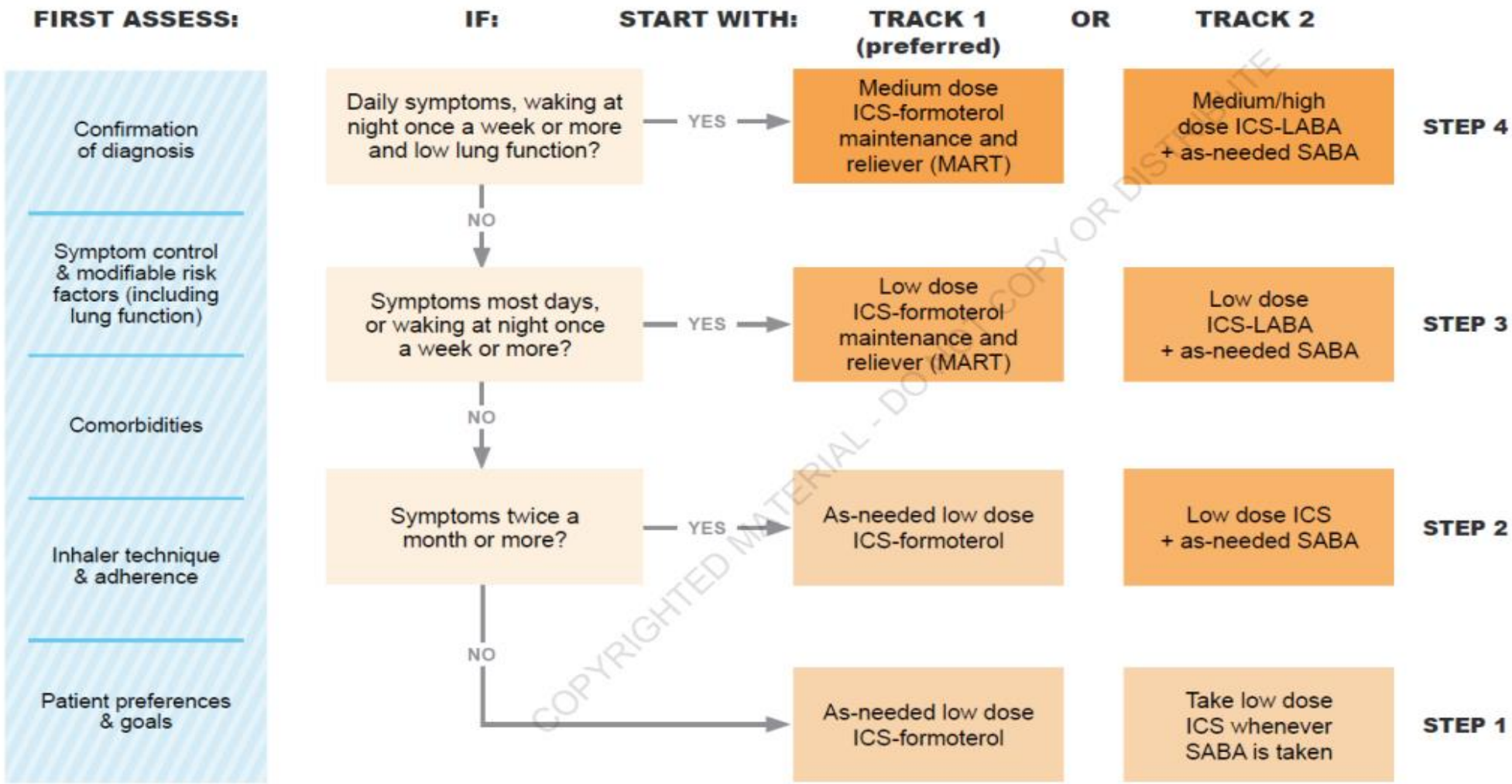
- Should be initiated as soon as possible after the diagnosis
- Early initiation of low dose ICS greater improvement in lung function(symptoms >2yrs).
- Patients not taking ICS decline in lung function than those who are taking ICS.
- Occupational asthma - increase the probability of resolution of symptoms, and improvement of lung function and airway hyper responsiveness.

After starting initial controller treatment

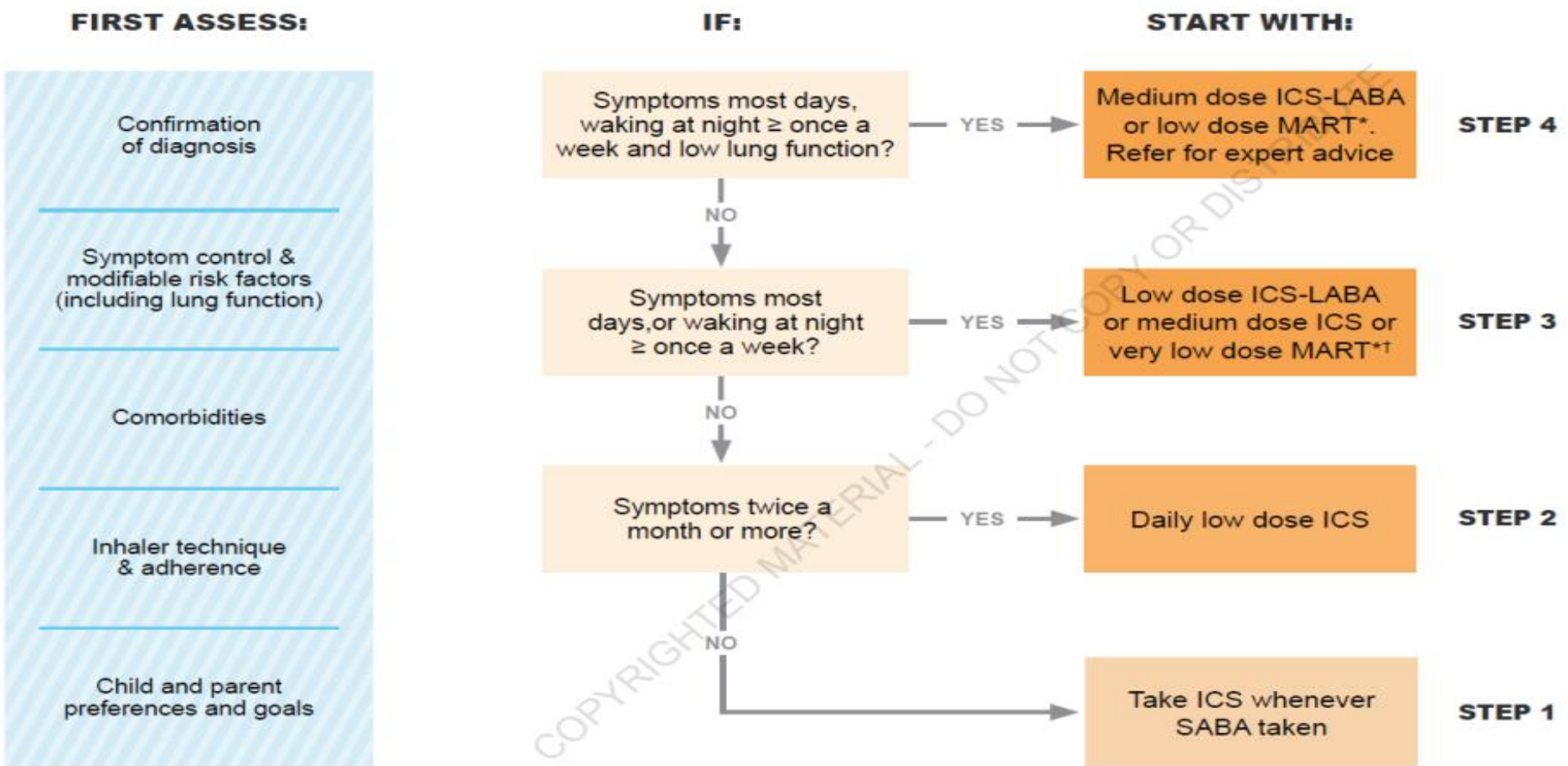
- Review child's response after 2–3 months, or earlier depending on clinical urgency.
- Check adherence and inhaler technique frequently.
- Step down treatment once good control has been maintained for 3 months.

STARTING TREATMENT

in adults and adolescents 12+ years with a diagnosis of asthma



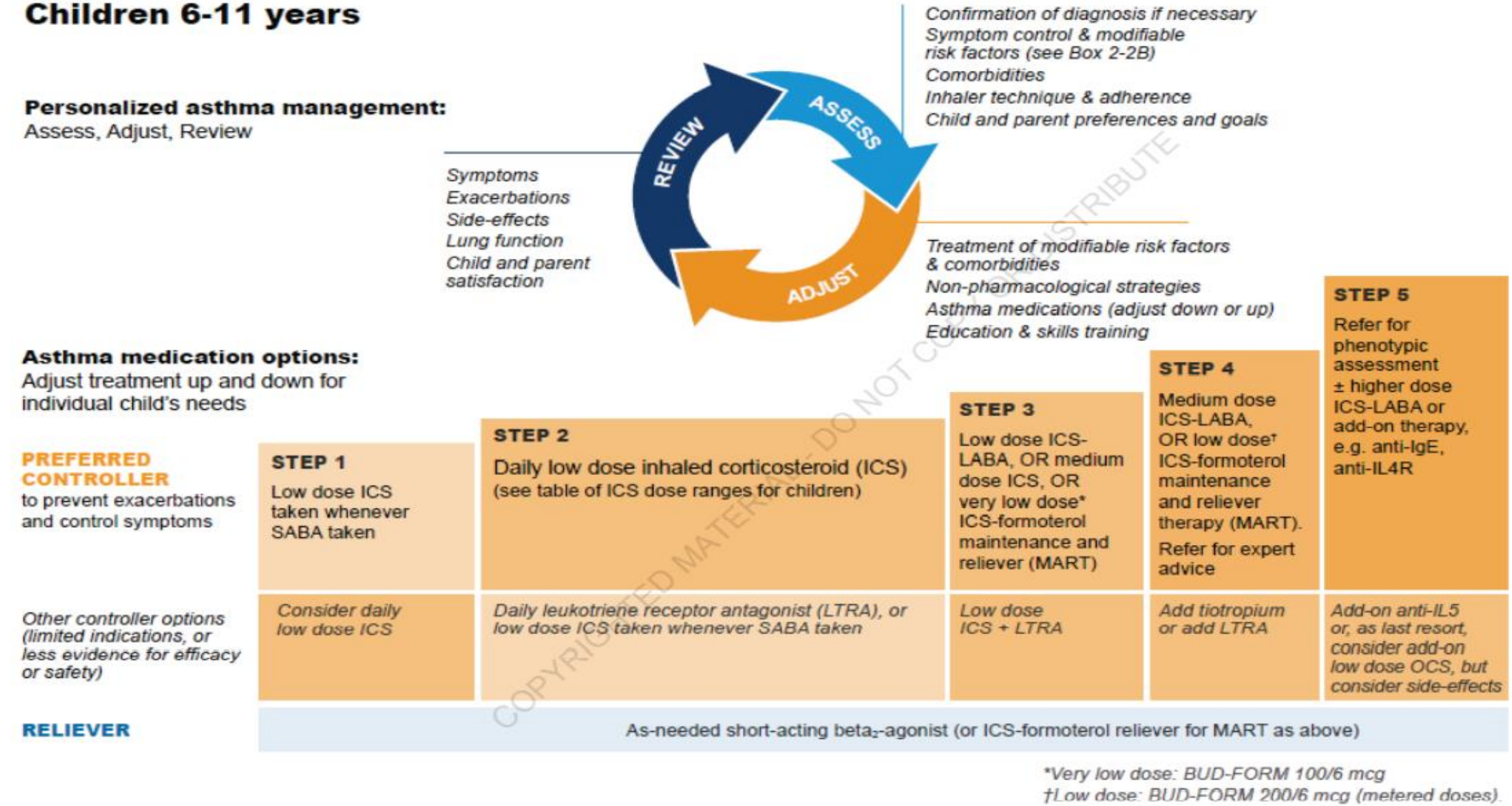
Box 3-4Dii. Selecting initial controller treatment in children aged 6–11 years with a diagnosis of asthma (V2)



Persisting uncontrolled symptoms and/or exacerbations despite 2–3 months of controller treatment

- Incorrect inhaler technique
- Poor adherence
- Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or NSAIDs.
- Comorbidities that may contribute to respiratory symptoms and poor quality of life
- Incorrect diagnosis

Box 3-5B. Personalized management for children 6–11 years to control symptoms and minimize future risk

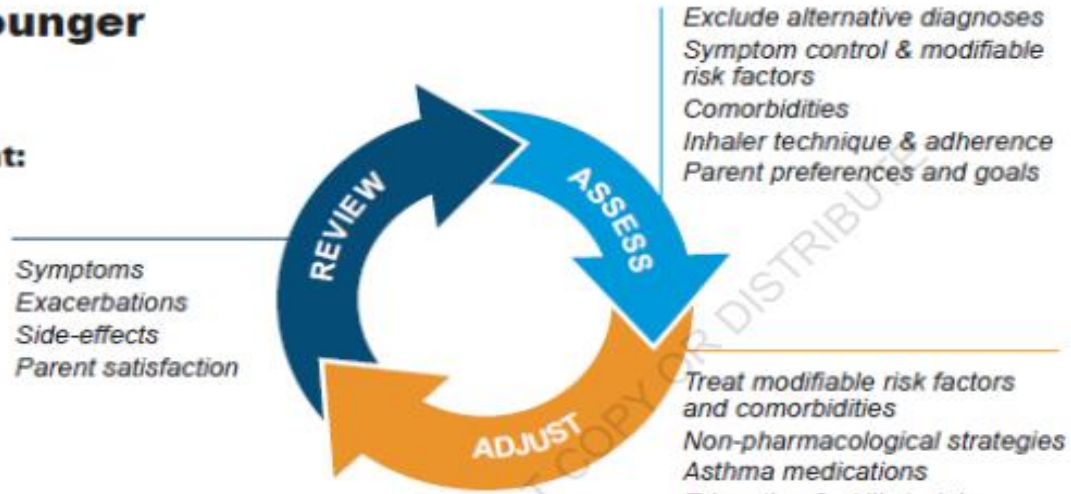


BUD-FORM: budesonide-formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. For *initial* asthma treatment in children aged 6–11 years, see Box 3-4C (p.58) and Box 3-4D (p.59)
See Box 3-6, p.63 for low, medium and high ICS doses in children.

Box 6-5. Personalized management of asthma in children 5 years and younger

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

	CHILDREN 6-11 YRS	**0-5 YRS OLD**
STEP 1	LOW DOSE ICS+SABA,DAILY LOW DOSE ICS	INTERMITTENT SHORT CIURSE ICS
STEP 2	DAILY LOW DOSE ICS, DAILY LTRA, ICS+SABA	DAILY LOW DOSE ICS, DAILY LTRA + INTERMITTENT SHORT COURSE ICS
STEP 3	LOW DOSE ICS- LABA OR MEDIUM DOSE ICS , VERY LOW DOSE ICS-FOEMETEROL(MART), LOW DOSE ICS+ LTRA	DOUBLE LOW DOSE ICS, LOW DOSE ICS + LTRA
STEP 4	MEDIUM DOSE ICS-LABA,LOW DOSE MART, +IPRATROPIM BROMIDE OR LTRA	CONTROLLER & RELIVER + LTRA, INCREASE ICS FREQUENCY
STEP 5	HIGH DOSE ICS – LABA, ADD ON THERAPIES	

Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.166)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; n.a. not applicable; pMDI: pressurized metered dose inhaler; ICS by pMDI should preferably be used with a spacer.

Inhaled corticosteroid	**Low total daily dose (mcg)** (age-group with adequate safety and effectiveness data)
BDP (pMDI, standard particle, HFA)	100 (ages 5 years and older)
BDP (pMDI, extrafine particle, HFA)	50 (ages 5 years and older)
Budesonide nebulized	500 (ages 1 year and older)
Fluticasone propionate (pMDI, standard particle, HFA)	50 (ages 4 years and older)
Fluticasone furoate (DPI)	Not sufficiently studied in children 5 years and younger)
Mometasone furoate (pMDI, standard particle, HFA)	100 (ages 5 years and older)
Ciclesonide (pMDI, extrafine particle, HFA)	Not sufficiently studied in children 5 years and younger

BDP: beclometasone dipropionate; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); in children, pMDI should always be used with a spacer

Choice of medication, device and dose

- Based on assessment of,
  - symptom control
  - risk factors
  - Preference
  - practical issues (cost, ability to use the device, and adherence)
- Monitor response & side effects → adjust the dose.
- Good symptom control (2–3 months) → titrate ICS dose.
- The ICS-containing medication should be taken every day or, in mild asthma, an alternative is to take as-needed low dose ICS-formoterol for symptom relief.

REVIEWING RESPONSE AND ADJUSTING TREATMENT

- Patients be seen 1–3 months after starting treatment and every 3–12 months after that.
- After an exacerbation → review within 1 week
- The frequency of review depends on the
  - Patient's initial level of symptom control
  - Their risk factors
  - Their response to initial treatment
  - Their ability and willingness to engage in self-management with an action plan.

STEPPING UP ASTHMA TREATMENT

- Sustained step-up :
  - If symptoms and/or exacerbations persist despite 2–3 months of controller treatment.
    - Incorrect inhaler technique
    - Poor adherence
    - Modifiable risk factors, e.g. smoking
    - Symptoms due to Co morbid conditions, e.g. allergic rhinitis
- Short-term step-up
  - (for 1–2 weeks) by clinician or by patient with written asthma action plan e.g. during viral infection or allergen exposure
- Day-to-day adjustment
  - By patient in GINA Track 1 , with as-needed low dose ICS-formoterol for mild asthma, or ICS-formoterol as maintenance and reliever therapy (MART) for moderate-severe asthma. This is particularly effective in reducing severe exacerbations

STEPPING DOWN TREATMENT

- Choose an appropriate time for step-down (no respiratory infection, patient not travelling, not pregnant).
- Assess risk factors, including history of previous exacerbations or emergency department visit, and low lung function.
- Document baseline status (symptom control and lung function), provide a written asthma action plan, monitor closely, and book a follow-up visit.
- Step down through available formulations to reduce the ICS dose by 25–50% at intervals of 2–3 months.
- If asthma is well controlled on low dose ICS or LTRA, as-needed low dose ICS-formoterol is a step-down option.
- Do not completely stop ICS in adults or adolescents with asthma unless this is needed temporarily to confirm the diagnosis of asthma.
- Make sure a follow-up appointment is arranged.

OTHER THERAPIES

- Allergen immunotherapy
  - Subcutaneous immunotherapy (SCIT)
  - Sublingual immunotherapy(SLIT)
- Vaccinations
- Bronchial thermoplastic
- Vitamin D

NON-PHARMACOLOGICAL STRATEGIES

- Smoking cessation
- Physical activity
- Investigation for occupational asthma
- Identify aspirin-exacerbated respiratory disease
- Avoidance of medications that may make asthma worse
- Healthy diet
- Avoidance of indoor allergens
- Avoidance of outdoor allergens
- Breathing exercise

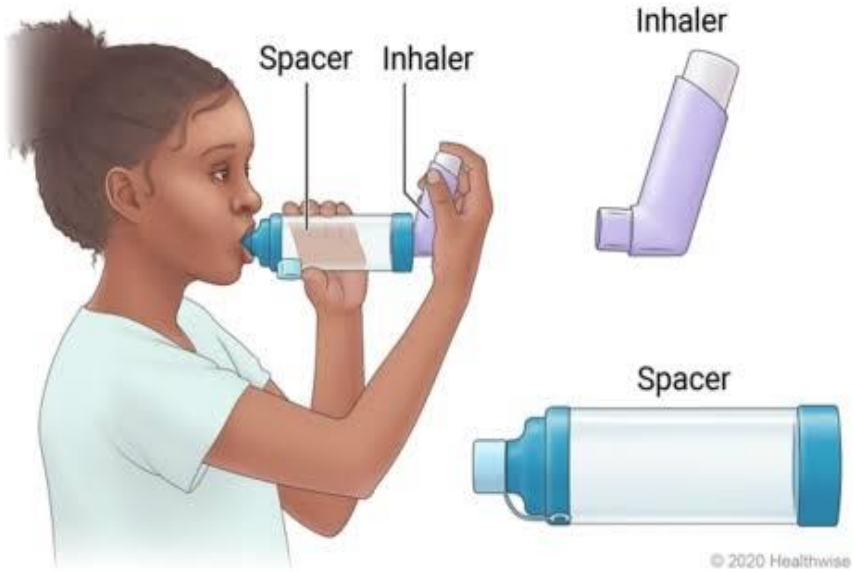
STEPS IN EFFECTIVE USE OF INHALER DEVICES

METERED DOSE INHALER

- Shake inhaler before use. Remove the cap. Prime it before using first time.
- Breathe out away from the inhaler
- Bring the inhaler to your mouth and seal the mouth piece with the lips.
- Breathe in slowly and press the medicine button and keep breathing .
- Remove inhaler and hold the breathe for 10sec and breathe out.
- If need another puff wait another 30sec and repeat same
- Wash your mouth after use.
- Store at room temp.
- Remove the metal part and wash the plastic parts with mild soap and water and air dry it. Then fix it and test the dose by air spraying it before use.

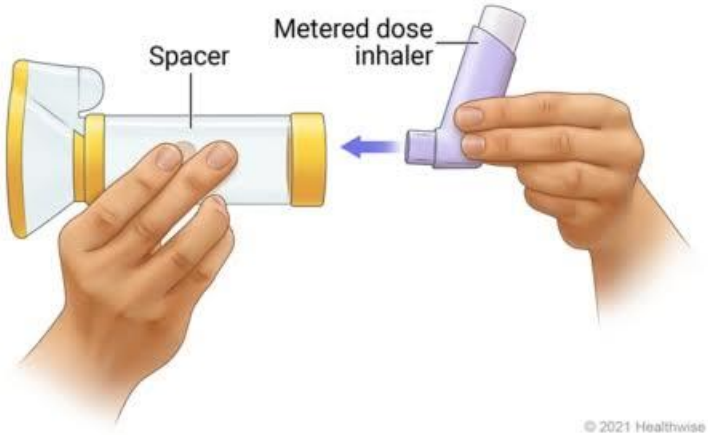
WITH SPACER

- Shake the inhaler and attach it with the spacer.
- Breathe out away from inhaler and then seal the inhaler with the lips.
- Add the medication and then take slow breaths until full breathe and then take 5 short breathes. Slowly breathe in and hold for 10 sec. If hearing whistle sound you are breathing too fast and so take slowly breathes.
- Separate the spacer and then Clean the spacer with warm water and mild soap
- Rinse it in clean water
- Air dry it. Do not use towel
- Use only one puff at a time in the spacer.
- Do not share the spacer.
- Use only with pressurised inhaler not with dry powders
- If damaged do not use it. Take another one
- Keep away from heat sources



REVOLIZER

- Hold it in the hand and then open the mouth piece completely.
- Place the rotacaps inside the hole by placing the transparent face downside.
- Close the mouthpiece and then breathe out
- Place REVOLIZER in the mouth and then inhale through mouth and after completion remove it and hold breathe for 10sec
- After use, remove empty rotacaps
- Clean REVOLIZER once a week usually it's mouth piece and hole by using running water
- Shake ton remove excess water and then air dry it.


Spacer
Metered dose inhaler
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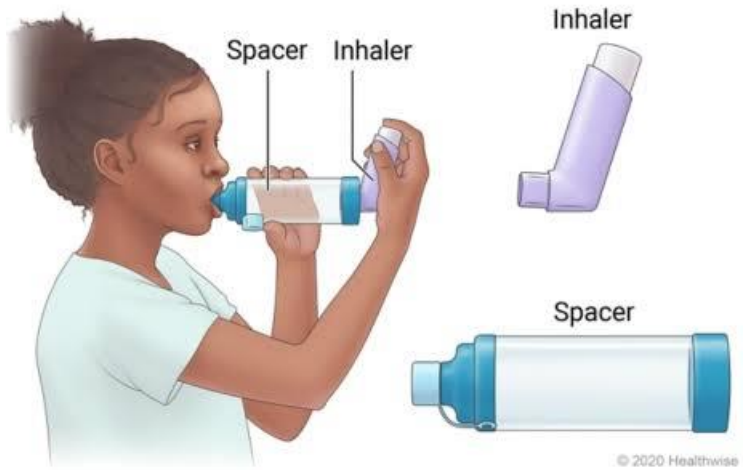
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Inhaler
Inhaler
Spacer
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open the mouthpiece fully till both arrows meet
revolizer
Cipla


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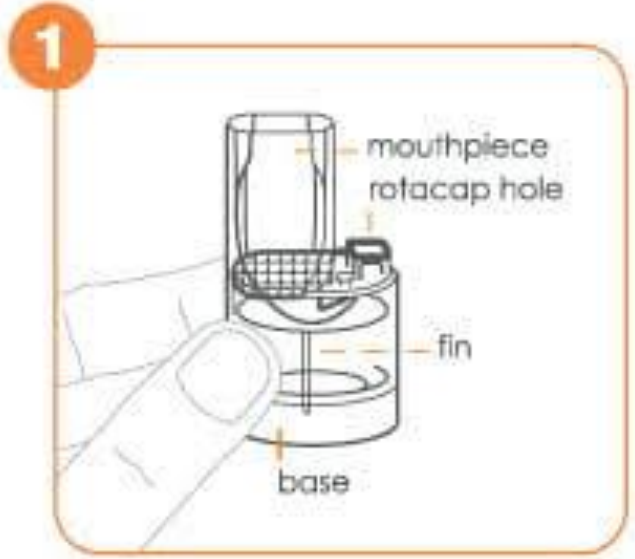

1
mouthpiece
rotacap hole
fin
base


30 capsules
Cipla
foracort
rotacaps®
400
with rotahaler®/revo
30 capsules
Cipla
Formoterol Fumarate and
Budesonide Powder for Inhalation IP
foracort
rotacaps®
400


Seretide
ACCUHALER
1460925
GlaxoWellcome


Fluticasone and Salmeterol
Inhalation Powder, pre-metered BP
28 Blisters

TOP 10
INHALER MISTAKES

Inhaled asthma medicine needs to reach the airways to work. Here are 10 common mistakes made when using a metered-dose inhaler (MDI) and how to correct them.

1 SITTING DOWN
FIX IT: Standing allows the lungs to fully inhale and provides more power to exhale.

2 USING AN EMPTY INHALER
FIX IT: Request a refill when the inhaler is half full so you never run out.

3 NOT SHAKING OR PRIMING THE INHALER
FIX IT: Shake the inhaler canister 10 to 15 times for the medication to be ready to work. When using a new inhaler, prime it by releasing three to four test sprays. Prime again if not used for several weeks.

4 NOT USING A SPACER WITH AN MDI INHALER
FIX IT: A spacer helps deliver the medication to the airways instead of the mouth. Insert the inhaler into the spacer. Spray one puff of medicine and inhale slowly. Hold your breath for a count of 10 and exhale slowly.

5 HOLDING THE HEAD TOO FAR FORWARD OR BACKWARD
FIX IT: The head needs to be in a normal position, not too far back or too far forward, to help make a direct path for the medicine to reach the airways.

6 TONGUE OR TEETH IN THE WAY OF SPACER/INHALER OPENING
FIX IT: Put the spacer/inhaler in the mouth above the tongue, under the top teeth.

7 MOUTH NOT TIGHT ENOUGH AROUND SPACER/INHALER
FIX IT: Close the lips around the spacer so air does not escape.

8 DIRECTING SPACER/INHALER AT TONGUE OR ROOF OF MOUTH
FIX IT: Aim the spacer/inhaler at the back of the throat, so the medicine reaches the lungs.

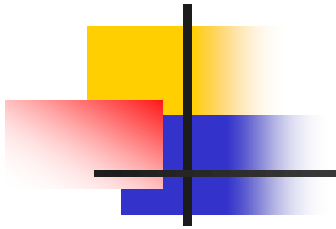
9 SPRAYING SEVERAL PUFFS OF INHALER INTO SPACER
FIX IT: Spray only one puff of the inhaler at a time into the spacer. Breathe out before inhaling. Hold breath for a count of 10, then exhale. Repeat for the number of puffs the doctor prescribed.

10 INHALING MEDICINE TOO FAST
FIX IT: Inhale slowly. A whistle from the spacer means the inhalation is too fast.

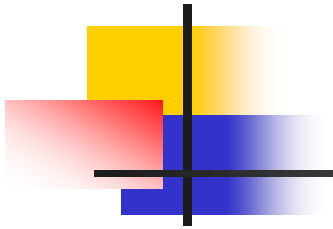
APPLICATION OF GINA IN PEDIATRIC POPULATION

- A 8 yrs old male child admitted in the emergency department of the hospital with complaints of shortness of breath and cough for past 3 days
- On examination showed a silent chest, an elevated esonophils count and spO2 level of 93%.

- What are the treatment options available for the child?



- Corticosteroids :-
- Nebulisation with bronchodilators
- Antibiotics :-



THANK YOU

MICROBES AND ANTIBIOTICS

by

Sneha susan joshy

pharm d intern

GRAM-ve	GRAM+ve ORGANISMS	ANAEROBIC
Escherichia Haemophilus(B) Klebsiella Meningococcus gonococcus Actinobacillus(B) Aeromonas(B) Brucella Citrobacter Enterobacter Enterobacteriaceae Francisella Legionella Neisseria Pseudomonas Salmonella Shigella Vibrio	Staphylococcus Streptococcus Enterococcus Micrococcus Mycobacterium tuberculosis Clostridium botulinum Corynebacterium diphtheria Clostridium tetani Bacillus anthrax	Actinomyces—GP Bacteroides—GN Clostridium—GP Fusobacterium—GN Lactobacillus—GP GP = Gram-positive GN = Gram negative

COMMON BACTERIA AND INFECTIONS

- RESPIRATORY TRACT INFECTIONS- GRAM+ve(STREPTOCOCCUS,HAEMOPHILUS)
- SKIN IFECTIONS -GRAM -ve (STAPHYLOCOCCAL)
- URINARY TRACT INFECTIONS -GRAM NEGATIVE(ECOLI)

All cocci are +ve except meningo,gono

All bacilli are –ve except DATA(diphteria,actinomyces,tetanus,anthrax)

ANTIMICROBIAL RESISTANCE

unresponsiveness of m.o to an AMA

- MDR(multidrug resistance)

Non susceptibility to atleast one agent in 3/more antimicrobial categories

Bacteria that resist treatment with more than one antibiotic are called MDROs

Eg:MRSA(methicillin resistant staphlococus aureus)

VRSA

- XDR(extensively drug resistance)

Non susceptibility to atleast one agent in all but 2/fewer antimicrobial categories

- ESBLs(extended spectrum beta lactamase producers)

gram negative organisms(enterobacteriacea,klebsilla,ecoli)

Inactivate beta lactum type antibiotics

- NDM- new delhi metallo betalactamse 1

enzyme that make bacteria resistant to broad range of beta lactum antibiotics

Eg: gram negative –ecoli, klebsilla

- CRA(carbapenem resistant Acinetobacter baumani)

Resistant to nearly all antibiotics

- CRE (carbapenem resistant enterobacteriacea)

resistant to an antibiotic class(carbapenems)

Classification of Antibiotics

Based on mode of Action

- Bacteriostatic
- Bactericidal

Based on their spectrum of action

- Broad-spectrum
- Narrow Spectrum

BASED ON MODE OF ACTION

BACTERIOCIDAL(kill)

Inhibition of cellwall synthesis

PENCILLINS,CEPHALOSPORINS,AMINOGLYCOSIDES,VANCOMYCINS,

FLUROQUINOLONES,RIFAMPICIN,METRONIDAZOLES

"P &C Are Very Cidal For Real Microbes"

BACTERIOSTATIC(prevent)

inhibition of protein synthesis

SULFAMETHOXAZOLE,TETRACYCLINES,TRIMETHOPRIM,ERYTHROMYCIN,LINEZOLID

CHLORAMPHENICOL,CLINDAMYCIN

STTEL -CC

BASED ON SPECTRUM

- NARROW SPECTRUM

Lincosamides(lincomycin,clindamycin),Glycopeptides(vancomycins,teicoplainin),Aminoglycosides(strepto,genta,amikacin),macrolides(erythro, clarithro,azithro)

LIGAMent/GLAM

BROAD SPECTRUM

Tetracyclines(doxycycline),cephalosporins, pencillin,chloramphenicol,fluroquinolones(ciprofloxacin,nor) sulphonamides

Antibiotic Classes

Gram Coverage

1. AmiNOglycosides - Gram (-) = NO
2. Cephalosporins - Gram (+)/(-)
3. Tetracyclines - Gram (+)/(-)
4. Penicillins - Gram (+)/(-)
5. Sulfonamides - Gram (+)/(-)
6. Fluoroquinolones - Gram (+)/(-)
7. Macrolides - Gram (+)
8. Carbapenems - Gram (+)/(-)
9. Lincosamides - Gram (+)
10. Glycopeptides - Gram (+)

GLAM

CEPHALOSPORINS

Antimicrobial	First-Generation	Second-Generation	Third-Generation	Fourth-Generation	Fifth-Generation	Cephalosporin/ β-Lactamase Inhibitor
Examples	Cefadroxil (PO) Cefazolin (IV) Cephalexin (PO)	Cefaclor (PO) Cefotetan (IV) Cefoxitin (IV) Cefprozil (PO) Cefuroxime axetil (PO) Cefuroxime sodium (IV)	Cefdinir (PO) Cefditoren (PO) Cefixime (PO) Cefotaxime (IV) Cefpodoxime proxetil (PO) Ceftazidime (IV) Ceftriaxone (IV, IM)	Cefepime (IV)	Ceftaroline (IV)	Ceftazidime/ avibactam (IV) Ceftolozane/tazobactam (IV)
Mechanism of Action	Inhibits cell wall synthesis					β-lactamase inhibitor binds to β-lactamase, prevents it from breaking down cephalosporin Inhibits cell wall synthesis
Spectrum of Activity	**Gram +:** *Staphylococcus* (except MRSA and MRSE), *Streptococcus*	**Gram +:** *Staphylococcus* (coverage not as good as first-generation) and *Streptococcus* (slightly better than first-generation)	**Gram +:** *Staphylococcus* (No MRSA or MRSE) and *Streptococcus*	**Gram +:** *Staphylococcus* (No MRSA or MRSE) and *Streptococcus*	**Gram +:** *Staphylococcus* (including MRSA, MRSE, VRSA) and *Streptococcus*	**Gram +**: *Streptococcus*

(continued)

Antimicrobial	First-Generation	Second-Generation	Third-Generation	Fourth-Generation	Fifth-Generation	Cephalosporin/ β-Lactamase Inhibitor
Spectrum of Activity *(Cont'd)*	**Gram –:** *E. coli, Klebsiella,* and *Proteus mirabilis*	**Gram –:** *E. coli, Klebsiella, Proteus, Neisseria, Moraxella, H. influenzae*	**Gram –:** *E. coli, Klebsiella, Proteus, Neisseria, Moraxella, Haemophilus, Salmonella, Shigella* (Note: Most *Enterobacteriaceae* are covered)	**Gram –:** *Enterobacteriaceae, Moraxella, Haemophilus, Neisseria* Better gram (–) coverage than the third-generation, including *Pseudomonas* and stable against some AmpC-producing β-lactamases	**Gram –:** Similar to third-generation; *Enterobacteriaceae, Haemophilus, Moraxella, Neisseria*	**Gram–**: *E. coli, Klebsiella, Proteus, Enterobacter, Citrobacter, Providencia, Pseudomonas*
	Anaerobes: *Actinomyces Lactobacillus, Peptococcus, Peptostreptococcus, P. acnes*	**Anaerobes:** *Peptococcus, Peptostreptococcus, P. acnes,* cefoxitin and cefotetan have broad anaerobic coverage including *B. fragilis;* however, resistance is increasing	**Anaerobes:** *Peptococcus, Peptostreptococcus, P. acnes,* cefotaxime and cefoperazone have some gram-negative anaerobic activity; however, not *B. fragilis*	**Anaerobes:** No reliable coverage	**Anaerobes:** No reliable coverage	**Anaerobes:** Broad including *B. fragilis* (ceftolozane/ tazobactam only)
	Atypical: None	**Atypical:** None	**Atypical:** None	**Atypical:** None	**Atypical:** None	**Atypical:** None
Spectrum of Activity Summary	Ceftaroline is the only cephalosporin with MRSA activity. No enterococcal activity across the class. In general, as you increase in generation you gain better gram-negative activity. Ceftazidime, cefepime, ceftazidime/avibactam, and ceftolozane/tazobactam cover *Pseudomonas*. Cefoxitin, cefotetan, cefotaxime, and cefoperazone have good anaerobic activity. Ceftazidime/avibactam and ceftolozane/tazobactam have activity against some carbapenemase-producing organisms.					

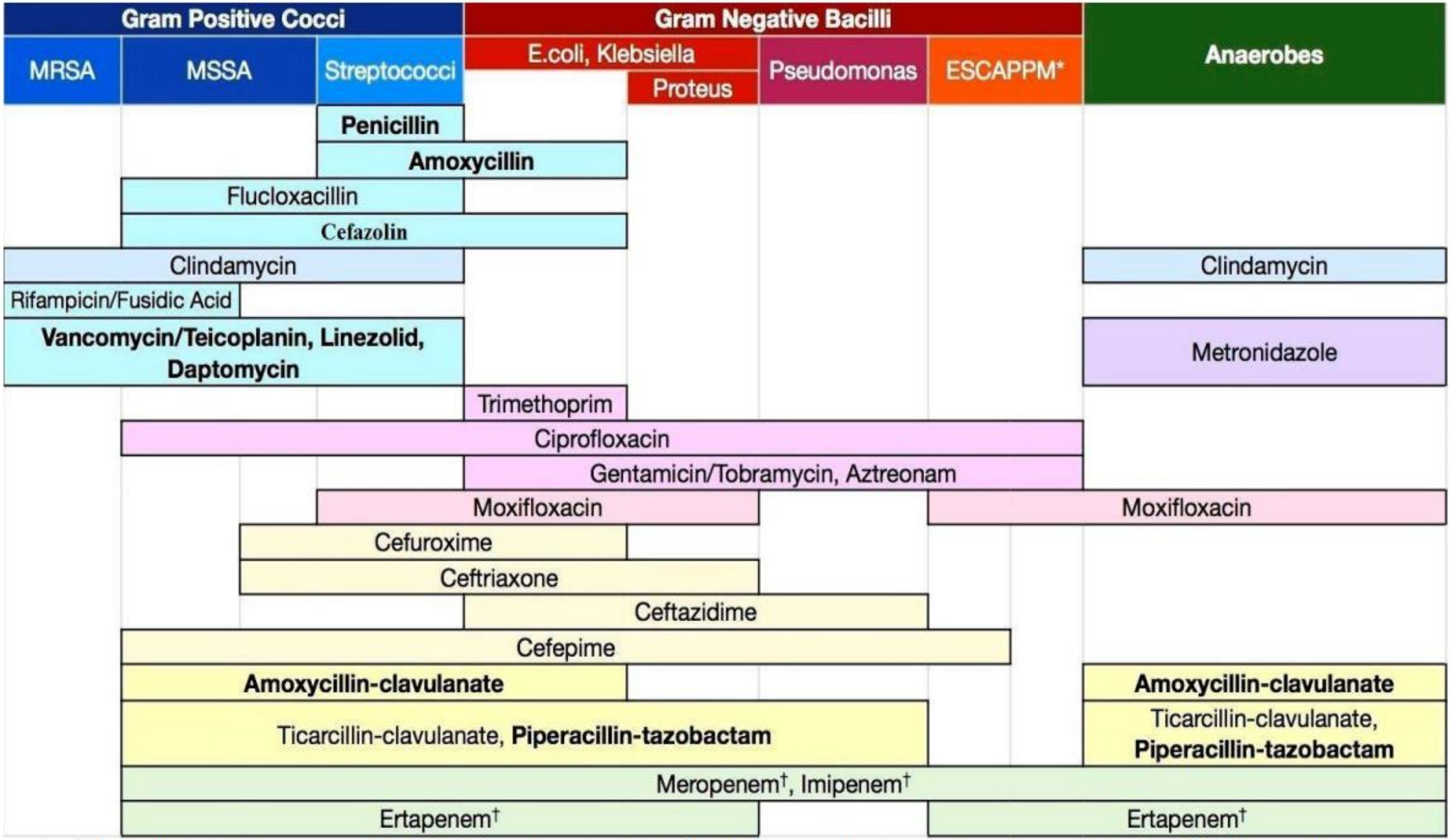
BETA LACTAMASE INHIBITORS

- Beta lactamases are family of enzymes produced by many gram

+ve and gram –ve bacteria that inactivate b-lactam antibiotics by opening b-lactum ring

Beta lactamase inhibitors binds to beta lactamase prevent its from breaking down cephalopsorins inhibits cell wall synthesis

- Clavulanic acid
- Sulbactum
- Tazobactum


Gram Positive Cocci
Gram Negative Bacilli
MRSA
MSSA
Streptococci
E.coli, Klebsiella
Proteus
Pseudomonas
ESCAPPM*
Anaerobes
Penicillin
Amoxycillin
Flucloxacillin
Cefazolin
Clindamycin
Clindamycin
Rifampicin/Fusidic Acid
Vancomycin/Teicoplanin, Linezolid, Daptomycin
Metronidazole
Trimethoprim
Ciprofloxacin
Gentamicin/Tobramycin, Aztreonam
Moxifloxacin
Moxifloxacin
Cefuroxime
Ceftriaxone
Ceftazidime
Cefepime
Amoxycillin-clavulanate
Amoxycillin-clavulanate
Ticarcillin-clavulanate, Piperacillin-tazobactam
Ticarcillin-clavulanate, Piperacillin-tazobactam
Meropenem†, Imipenem†
Ertapenem†
Ertapenem†

Antibiotics for gram +ve	**Antibiotics for gram –ve**	**Anaerobic**
Vancomycin	Ampicillin + sulbactam	metronidazole
Ciprofloxacin	cefazolin	Carbapenems
Chloramphenicol	cefuroxime	Cholramphenicol
Levofloxacin	meropenam	tigecycline.
Gentamicin	ciprofloxacin	Clindamycin
Pencillin	Linezolid	
Clindamycin		

Amoxicillin-clavulanate
Ticarcillin-clavulanate
Piperacillin-tazobactum
Merpenem,imipenem

} *gram +ve,gram –ve, anaerobs*

ciprofloxacin } *gram+ &-ve*

metronidazole } *anaerobic*

ANTIBIOTIC USE

1. Making a clinical diagnosis
2. Limiting empiric antibiotic therapy
3. Know your bugs
4. Choose appropriate antibiotic
5. De escalation/ modification
6. Stop antibiotics in some situations
7. Reduce duration of therapy

RESPIRATORY ANTIBIOTICS PRESCRIBED IN PEDIATRICS

AGE CATEGORY

Age-group	Age
Newborn	0 days to 1 month
Infant	1 month to 1 year
Toddler	1 to 3 years
Preschool	3 to 6 years
School age child	6 to 12 years
Adolescent	12 to 18 years

UPPER RESPIRATORY TRACT INFECTIONS (URTI)

DIAGNOSIS	CAUSATIVE AGENT	FIRST LINE	SECOND LINE /ALTERNATIVE
RHINITIS	Viral -RSV Stre.pneumonia,H. influenza	Self limiting, symptomatic treatment Antimicrobial therapy not needed	
PHARYNGITIS	Viral/bacterial	Amoxicillin	Cephalexin(10 days) Azithromycin(5days)
TONSILITIS	Bacterial	“	“
OTITIS MEDIA	Pneumococci,H.influenza	Amoxicillin(80-90mg/kg/day)	Co-amoxiclav(80-90mgkg/day) Cefuroxime Cefpodoxime Ill patient with vomiting-Ceftriaxone for 3days(50mg/kg/day)
SINUSITIS	Bacterial	Amoxicillin	“
EPIGLOTITIS/LARYNGITIS	H.influenza	Airway, suction,CPAP Ceftriaxone(100mg/kg/day) Cefotaxime)(200mg/kg/day	

LOWER RESPIRATORY TRACT INFECTION(LRTI)

DIAGNOSIS	CAUSATIVE AGENT	FIRST LINE		SECOND LINE
COMMUNITY ACQUIRED PNEUMONIA	Bacterial/Viral	< 3 months	**IV**: always Cefotaxime± Gentamycin/ Amikacin Ceftriaxone	**IV**:Pipracillin-tazobactum ± Gentamycin/ Amikacin Cefoperazone –sulbactum ± Gentamycin/ Amikacin
	Pneumococci,H.influenza	3m -5yrs	**ORAL**: Amoxicillin **IV**: Ampicillin	**ORAL**: Co-amoxiclav/ Cefpodoxime/ Cefuroxime **IV**: Co-amoxiclav/ Cefotaxime/ Ceftriaxone
	Pneumococci,Mycoplasma	> 5yrs	**ORAL**: Amoxicillin **IV**: Ampicillin	**ORAL**: Co-amoxiclav/ Cefpodoxime/ Azithromycin **IV**: Co-amoxiclav/ Cefotaxime/ Ceftriaxone/ Azithromycin
HOSPITAL ACQUIRED PNEUMONIA		Piperacillin+Tazobactum(80mg/10mg/kg/day) Q6hrs Cefoperazone-sulbactum Cefepime Meropenem		

PENCILLINS

- **AMOXICILLIN**

Usual dose: oral- 25-50mg/kg/day in divided doses(bd)

suspecting S.pneumonia-45-90mg/kg/day bd

Brand names: Tab.Mox kid 125mg

Tab.Moxikind CV -500mg

syp.Mox redimix(250/5)

AMOXICILLIN +CLAVULANIC ACID

Usual dose: oral -25-50mg/kg/day in divided doses(bd)

IV -50-100mg/kg/day bd

Brand names: Tab.Advent 625mg(500+125)

tab. Augmentin Duo 625mg

syp Advent forte –(400/5)

syp Augmentin Duo (200/5)

- **AMPICILLIN**

Usual dose : 100mg/kg/day TIDorQID

CEPHALOSPORINS

- **First generation**

p/o: cephalexin -20-50mg/kg/day Q6-Q8hrs

SYP.SPORIDEX 125mg/5ml,250mg/5ml

Max dose:1g

gram +ve,gram -ve

atypical

- **Second generation**

p/o: cefuroxime axetil -30mg/kg/day bd

Cefakind 12mg, 250mg,500mg

Wakcef 500mg

Iv:cefuroxime Na-50- 100mg/kg/day Q8hrs(TID)

staphlyo-coverage

not good as 1st gen

streptoc-slightly

better than 1st gen

- **Third generation**
- **ORAL**

Cefixime

Usual dose**:** oral – 8mg/kg/day bd

syp. Taxim o(50/5ml)

syp. Taxim o forte(100/5ml)

Cefpodoxime

Usual dose : 10mg/kg/day bd

Monocef o(100mg/5ml)

same as 1st gen

more gram –ve coverage

- **IV**

Ceftriaxone -50mg/kg/day bd/tid

Life threatening-100mg/kg/day

Cefotaxime-100mg/kg/day bd/tid

fourth generation

Cefipime(IV):100-10mg/kg/day in 3 divided dose

- **MACROLIDES**

AZITHROMYCIN

Usual dose: 10mg/kg/day OD

Max: 500mg

Brand names: SYP.AZEE 200mg/5ml

FLUROQUINOLONES

LEVOFLOXACIN

Usual dose: 10-15mg/kg/day in 2 divided doses PO/IV

AMINOGLYCOSIDES

Amikacin- < 3months-15 mg/kg/d, OD

3m-5yrs-100 mg/ kg/d, TID or QID

gentamicin :5–7 mg/kg/d, OD

A case on LRTI

- A 10 yr 29.2kg weighed male patient got admitted in pediatrics with chief complaints of fever,cough*3days and vomiting and lab report shows TC and crp was elevated and diagnosed as wheeze associated LRTI

Ip medications

Inj. Cefuroxime 750mg IV tds *5 days

Inj.ondansetron 5mg stat

Syp.Ascoril LS 5ml tds

Tab. Azithromycin OD*2 days

DISCHARGE MEDICATIONS

- Tab.Azithromycin ?
- Syp. Ascoril LS 5ml TDS
- Syp. Mefthal sos

CALCULATION


Thank
You

Tense

Present tense
Past tense
Future tense

Present tense

Simple Present tense

→ We using Simple present tense for discribing a habitual action / Daily rontine works.

→ And also use Simple present tense for discribing general truth.

Eg: The water boils at 100°
I believe in god.

→ We can denot our future using Simple present tense. Something that we fix already for our future.

Eg: Our school reopens in next week.
My daddy arrives tommorow

Eg: I read books everyday.
I play Cricket everyday.
I drink juice everyday.

I play basket ball everyday.
you play basket ball everyday
we play basket ball everyday
she plays basket ball everyday.
He plays basket ball everyday.

He	
She	plays
It	

I	play
You	
We	
They	

That means we use 's' in Singular Subject we skip 's' in plural subjects.

I and U first person Singular But we Consider it as plural.

Negative form / sentence (do not)

I play Cricket - I don't play Cricket
You play Cricket - You don't play Cricket
We play Cricket - We don't play Cricket
She plays Cricket - She doesn't play Cricket
He plays Cricket - He doesn't play Cricket.
(does not)

play + do = play
does + play = plays

Yes or no questions

(a) She doesn't play Cricket. (Answ)
Does she play Cricket ? (Ques)

(b) You play Cricket (ans)
Do you play Cricket ?

(c) He plays Cricket (ans)
Does he play Cricket ?

WH Questions ?

(What, where, when, why, How, Howmuch)

(a) Does she play Cricket ? (yes/no Ques)
Why does she play Cricket ?
When does she play Cricket ?
Where does she play Cricket ?

(b) Do you play Cricket ?
Why do you play Cricket ?
When do you play Cricket ?
Where do you play Cricket ?
How do you play Cricket ?

Question tags ? (Tagg, Tagging, Tagged)

(a) She plays Cricket. (statement)
Doesn't she ? (Tag Ques)

(b) You play Cricket (Statement)
Don't you ? (Tag Ques)

(c) He plays Cricket (stat)
Doesn't he ? (tag Qus)

- If statment is positive the tag Question should be negative.
- If statment is negative then tag Question should be positive

Eg:
(a) She doesn't play Cricket
does she ?
(b) He doesn't play Cricket
Does he ?
(c) We don't play Cricket
do we ?
(d) You don't play Cricket
do you ?

Continuous

Present Perfect tense

- Denotes Ctns a Continuing action.

Eg: I am drinking Coffee now
I am reading newspaper now
You are watching mobile now
She is dancing.
Mom is Cooking.

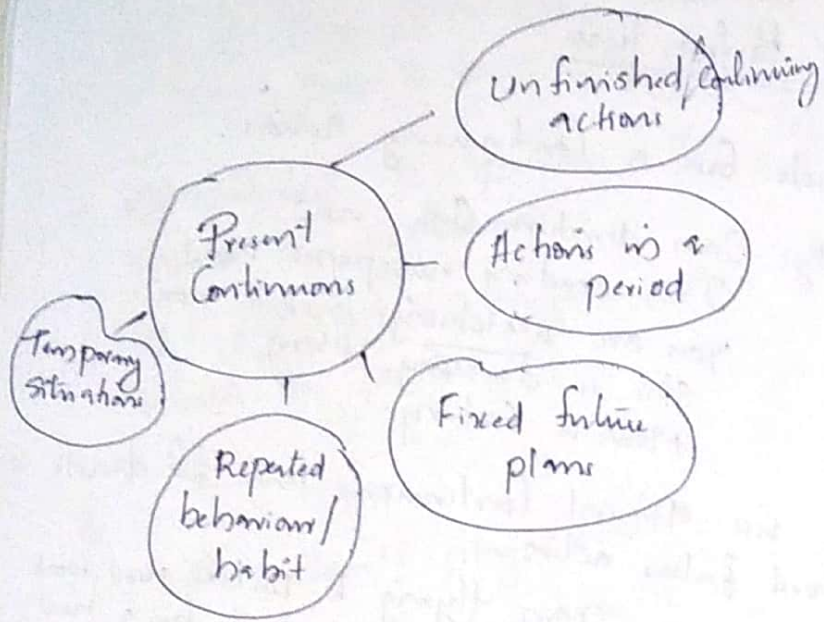
- We use Present Continuous tense to denote a fixed future action

eg I am flying to Dubai next week
My uncle is going to buy a car now
My sister is visiting grandma next month

- to denote actions in a period of time:
eg: They are preparing for the exam
He is practicing piano

- to denote Repeated behaviour
eg: He is always lying
She is always helping others
She is always coming late

- to denote temporary situations
eg: He is living in Calicut (not forever)



→ Subject + am/is/are + verb + ing

I	am	Verb+ing
He	is	
She		
It		
You	are	
We		
They		

Common mistakes in Present Continuous tense

Permanent status

eg: I am working as a teacher in Nirmala College ✗
He is working as a HR manager in ABC Company ✗

Here we use Simple Present tense

eg: I work as a teacher ✓
He works as a HR manger ✓

emotion / feelings

I am understanding ✗ I understand ✓
I am feeling ✗ I feel ✓
I am loving ✗ I love ✓

In case of Perceptions

(Hear, See etc..)

I am hearing ✗ I hear ✓

- Negative formation

(a) You are ~~watching~~ mobile (stat)
You are not watching mobile (neg)

(b) I am drinking Coffee (stat)
I am not drinking Coffee (neg)

(c) Mom is Cooking (stat)
Mom is not Cooking

(d) She is playing
She is not playing

(e) They are reading
They are not reading

- Yes or no Questions

(Just put the auxiliaries first)

(a) Are you watching mobile ? (Yes or no)
you are watching mobile. (statement)

(b) She is playing (statement)
Is she playing ?

(c) Man is Cooking (statement)
Is man Cooking ?

(d) They are reading newspaper (statement)
Are they reading newspaper.

- WH Questions

(a) Are you watching mobile ? (Yes/no)
why are you watching mobile ? (wh)

b) Are you drinking Coffee ?
Why are you drinking Coffee ?

c) Are they reading newspaper ?
When are they reading newspaper.

Present Perfect tense

Sub + has/have + been + ob
Sub + has/have + V3 + ob

- This tense link/Contact present and past time.
- Action in the past and effects in the present.

eg: ① lost my key (Simple past)
② have lost my key (Present perfect tense)

V1
is/am/are
do/does
has/have

V2
was/were
did
had

V3
Been
done
had

		V3
I You We They	have	lost
He She It	has	arrived

Sub + has/have + V3 + object

eg: ① have taught english
② have spoken english
My mother has drunk coffee

If don't mention the time it is Pre Per of do - Simple Pa

- Situations for Using Present Perfect tense

① To talk about life experience

eg: ① have never watched that movie
② have never visited America
③ have never tasted dragon fruit

② Finished actions / recent actions
(Recently finished action) eg: ① have just sent the mai
② have just finished the wo
He has just completed his wo

③ Just finished actions - Result in present
eg: I have Cooked the dinner
He has Completed his homework.

④ Unfinished actions (Still Continuing)
eg: I have worked here for 5 years
He has worked here since 2015

⑤ Unfinished time
(Today, this week, this month, this year)
eg: I haven't watched Tv today.

⑥ Repeated actions
eg: I have shopped here for 5 years.

Negative formation

Have + Not = Haven't
Has + not = Hasn't

eg: I haven't lost my key.
He hasn't lost his key.

Yes & No Questions

eg: Have you watched this movie?
Have you visited America?

Wh Questions

eg: How have you lost your key?
When have you lost your key?
(When did you lost your key) This is wrong Correct
Why have you lost your key?

Sub + has/have + V_3 + obj
Sub + has/have + been + Object.

- For Speak about an action/event.
① That started in the past and Continuous in the present
② To speak about our experience.
③ To speak about an action/event which is just Completed / finished
④ Action/event where time is not impotant to be mentioned.

eg: Athira & Ammu have lived in India for 20 & 25 years respectively.

Present Perfect Continuous tense

- Perfect + Continues = That means the action is Continuing
- Something started in the past has Continued and till now.
- In present perfect Something started in the past and its Consequence only happening now. Or in present perfect Continuous tense that action is still Continuing.
- Subject + has/have + been + V+ing

Eg. They have been talking for the last hour.
You have been waiting here for two hours

Simple Past tense / Past tense

(1) Formula

S + V2 + Ob
S + did + Ob
- S + was/were + Ob
S + had + Ob

Sub + V2 + Object

eg: I went to kollayam yesterday
I saw a film yesterday
watched

(2) Question word formula (WH)

Question word + did + Subject + Present tense + Object + ?

eg: What time did you sleep last night?
Who were your room-mates in the hostel?
What when did you birth?

(3) Yes/No Questions

Did + Subject + Present tense + object + ?

eg: Did you break a glass yesterday?

(4) was/were

Question word + was/were + object + ?

eg: who was your best friend before?
who were your best friends before?

⑤ Adjectives

[Was/were + Subject + adjective + object + ?]

eg. Was your father strict before?
Were your Parents strict before?

⑥ How many

[How many + Plural Subject + Were there + Object + ?]

How many students were there in your class last year?

S + had + ob
S + V2 + ob
S + did + ob
S + was/were + ob.

Past Continuous tense

① Formula

[Subject + was/were + Verb + ing + object]

eg. I was going for tution last year
We were going for tution last year
I was studying for pre-degree last year.

② Question word Questions

[Question word + was/were + Subject + Verb + ing + object + ?]

eg. How were you going for class those days?
How was he going for class those days?

③ Yes/No Questions

[Was/were + Subject + Verb + ing + object + ?]

eg. Was she going for tution those days?
Were they going for tution those days?

④ Who

[Who + was/were + Verb + ing + Object + ?]

eg. Who was attending the Seminar those days?
Who were attending the Seminar those days?.

⑤ How many

[How many + Plural Subject + were + verb + ing + Object + ?]

Eg. How many children were participating the Competition last week ?

8 Actions - talk about the first one

Past Perfect Tense   S + had + V^3 + Ob
S + had + been + Ob .

① Formula

[Subject + had + Past Participle + Object]

Eg: I had gone to Delhi five years ago
I had gone for tution last year

② Question word

[Question word + had + Subject + Past Participle + Object + ?]

Eg: What had you bought for me ?

③ Yes / No

[Had + Subject + Past Participle + Object + ?]

Eg: Had she Completed her examinations ?

④ Who

[Who + had + Past Participle + Object + ?]

Eg: Who had stolen money from the bag ?

⑤ How many

[How many + Plural Subject + had + past participle + Object + ?]

Eg: How many Children had done the homework ?

Past Perfect Continuous tense

(S + had + been + V + ing)

① formula

[Had + subject + been + verb + ing + object + ?]

Eg: Had you been working abroad for 10 years ?

Yes, answer

[Yes + subject + had been + verb + ing + object]

Eg: yes, I had been working abroad for 10 years.

No, answer

[No + subject + had not been + verb + ing + object]

Eg: No, I had not been working abroad for 10 years.

Simple future tense

① Formula

[Subject + will + Present tense of verb + Object]

Eg: I will go for mass tomorrow.
I will go to Kollam tomorrow.

② Question word

[Question word + will + Subject + Present tense + Object + ?]

Eg: When will you sleep tonight ?.

③ Yes / No Questions

[will + subject + Present tense + Object + ?.]

Eg: will you visit your friend tomorrow ?.

④ will be

[Question word + will + Subject + be + Object + ?]

Eg. Where will your Course be next year ?.

Adjective

[will + Subject + be + adjective + Object + ?.]

Eg: will your father be strict in the future ?.

⑥ How many

[How many + Plural Subject + will there be + Object + ?]

Eg: How many students will there be in your class next year ?.

Future Continuous tense

① Formula

[Subject + will be + verb + ing + object]

Eg: I will be studying for M.com next year
I will be going for tuition next year

② Question word

[Question word + will + Subject + be + verb + ing + object]

Eg: How will you be going for class next week

③ Yes/No qn

[will + Subject + be + verb + ing + object + ?]

Eg: will she be going for tuition next week?

④ Who

[Who + will be + verb + ing + object + ?]

Eg: who will be attending the Seminar next week?

⑤ How many

[How many + Plural Subject + will be + verb + ing + object + ?]

Eg: How many children will be participating in the Competition next week?

Future Perfect tense

① formula

Subject + will have + Past Participle + Object

Eg: I will have Completed my essay by next Tuesday.
I will have read that novel by next week.
They will have built their house by next year.
She will have written a book by April this year.

Type of Sentences

- There are 4 type of english Sentence classified By their purpose

+ve / -ve

assertive/answer

① Declarative Sentence (Statement) (It tells us Something)
② Interrogative Sentence (question) (It asks us Something)
③ Imperative Sentence (Command) (tell us to do Something)
④ exclamatory Sentence (exclamation) (It expresses surprise)

wish, advice, suggestion

① Declarative Sentence (.)

- It makes a Statement. They tell us Something, Give us information.
- Normally end with a full stop / period.
- Usual word order for the declarative Sentence is,
  - Sub + verb.
- It can be +ve / -ve

+ve	-ve
I like Coffee	I don't like Coffee
We watched TV last night	We didn't watch Tv last night

Eg: John likes Mary.

(2)

② Interrogative Sentence

- It asks a question / ask us something
- They want information
- Always end with a question mark.

• (wh-word +) auxiliary + Sub + Verb

Do you like Coffee ?	Don't you like Coffee ?
why did ye go ?	why don't you go ?

eg. Does Mary like John ?

③ Imperative Sentence (.) (!)

- It gives a Command
- and with full stop or period or exclamation mark

• Base Verb

Stop !	Do not stop !
Come her Coffee	Don't give her Coffee

eg. Stop ! Close the door.

④ Exclamative Sentence (!)
(Exclamation)

- Express strong emotion / Surprise
- end with an exclamation mark (!)

• What + adjective + Noun + Subject + verb

• How (+ adjective / adverb) + subject + verb

eg. What a liar he is !
What an exciting movie it was !
How he lied !
How exciting the movie was !

simple
compound
complex

classification / division / categorizing / grouping

- Preposition — eg. in, on, from, by, at, for
- Adverb
- Adjective
- Parts of speech
- Reported speech
- Voice.

Simple Past

→ (Sub + V_2 + object + Time word)

- Sub + was/were + object

eg

- Sb + had + object.
- Sub + did + object.

Past Continuous

Sub + was/were + V + ing + object.

India was developing (Country).

State of affair - Situation

Past Perfect tense

Sub + had + V_3 + object.

Sub + had + been + object.

eg: Athira had organized a huge newyearparty meeting before she went to Chennai.

I had been to goa before I went Tamilnadu.

Past perfect Continuous continuous

Sub + had + been + V + ing + object

Simple future

Sub + will + V_1 + object.

eg: I will scold him when he comes ~~to~~ home.
I will go for mass tomorrow.
I will go to munnar tomorrow ~~for~~ to enjoying my weekend.

Preparing.

~~Simple future~~

future Continuous continuous

Sub + will + be + V_1 + ing + object.

eg: I will be going to study on abroad for the coming next 2 years.

They will be Critizing his work until it is fulfilled. Criticizing

She will be describing about the topic until this class over. gets

Future perfect

Sub + have + been + V4

Sub + will have + V3 + Object

eg: She will have written a book by April this year.

They will have fullfilled their dreams by next year.

in - year, month, season

on - days, dates, special days

at - particular time

Preposition

1. On

Before days

(a) I want to kollam on Sunday
(b) My Birthday is on monday
(c) My Sister Came here on Friday

Before dates

(a) I was born on July 23, 1998
(b) India got Independence on 15 August 1947
(c) India became a republic on jan 26, 1950.

'up' on Something

(a) The pen is on the table
(b) She kept her bag on the bench
(c) He pasted a poster on the wall

Correct time

(a) The train's arrived on time
(b) The bus is on time
(c) The flight was on time this morning

in Bank.
at T

'walk'

(a) She came to school on foot
(b) They went home on foot

② In

Before places

(a) I am born in Idukki
(b) The prime minister wasn in kerala last
(c) Thajmahal is in Agra

Before years

(a) The British left India in 1947
(b) My grandpa died in 1993.

Before name of months

(a) He will return to Dubai in June
(Don't add in before last & next)
(b) My uncle came home last december
(c) Our classes will restart in september.

Morning, afternoon evening

(a) I pray in the morning everyday.
(b) We play cricket in the afternoon
(c) I bathe in the evening.

'rob'

(a) His father is the manager in a factory
(b) There are many lions in the forest

③ AT

Before time

(a) I get up at 5:30 every morning

Before small places

(a) I was born at kattappana in Idukki
(b) He is studying at kottayklal in Mukkam.

'night'

(a) My father is return at night.

'Home'

(a) My mother is at home now

Afternoon

(a) She reached here at noon.

④ To

ദിശ/ ചലനം

(a) She went to hospital this morning.

⑤ By

Before vehicles

(a) I go to my College by bus.
(b) He comes for holidays by train
(c) He went for a picnic by car.

Passive voice

(a) Gandi was killed by Godse
(b) Students were attacked by the police

⑥ From

ൻ്റ സ്ഥാനം

(a) She Came from hospital this afternoon
(b) He hired a taxi from the railwaystation

Time

(a) I waited for the bus from 9 o'clock to 10 o'clock

(b) The price of vegitables will increase from June 1

⑦ Of

ദേശ/ സ്ഥല/ വസ്തു

(a) Onam is a festival of Kerala
(b) Delhi is the Capital of India

FOR

⑧ ന്ന് / വേണ്ടി

(a) We went for a film yesterday.
(b) Students Come for tution at home every morning

Time duration

(a) He was working in Saudi for five years.

(b) I waited for him for almost an hour

⑨ With

കൂടെ/ സഹായം

(a) I went for a movie with my friend this morning.

(b) She was with her mother yesterday

Present Perfect Continuous

S + has/have + been + ing + obj

Past Perfect Continuous

S + had + been + ing + obj

Future Perfect Continuous

S + will/shall + have + been + V + ing + obj

Shall - I, we
will - I, we, you, he, she, it, they

Voice

Active	Passive
S + V + Ob	Ob + V + S
I	me
we	us
you	you
they	them
He	him
She	her
(Simple, Straight forward/Certain)	(Confusing/Complicated)

Simple Present tense

A : S + V+ ob
P : ob+ is/am/are + V3 + S

Sadiq writes a letter
A letter written by sadiq

A: Sadiq wears his watch. } Use only A.
P: (His watch ware by sadiq) wrong.

① Tell me about one good news you heared of received ? who gave the good news ? what was it ? when did you get it ? why you think that it is good ? how did you feel about?

Conditionals

- Zero conditional
- 1st
- 2nd
- 3rd
- 4th
- 5th / mixed conditions

Describe about a time when you met a stranger. when was it ? where how was, where, who?

Tell me about a time when somebody lies to you. who is that person ? why did ? How do you feel about ?

Talk about a person who encouragons a lot ?. who ? his/her personality ? what way ?. why you need ?

21 Saturday

Simple Present - പതിവായി ചെയ്യുന്ന ഒരു കാര്യത്തെ
S + V1 + Obj

Simple Past - കഴിഞ്ഞു പോയ ഒരു കാര്യത്തെ പറ്റി പറയാൻ
S + V2 + Obj

Simple future - വരാനിരിക്കുന്ന ഒരു കാര്യത്തെ പറ്റി
S + will + V1 + Obj

Present Continuous - ഇപ്പോൾ നടന്നുകൊണ്ടിരിക്കുന്ന
S + is/am/are + V1 + ing + Obj

Past Continuous - പണ്ട് നടന്നുകൊണ്ടിരുന്ന
S + was/were + V1 + ing + Obj

Future Continuous - ഭാവിയിൽ നടന്നുകൊണ്ടിരിക്കും എന്നു പറയുന്ന
S + will be + V1 + ing + Obj

Present Perfect - ഇപ്പോൾ ചെയ്തിട്ടുണ്ട്
S + has/have + V3 + Obj

Past Perfect - മുൻപ് ചെയ്തിട്ടുണ്ടായിരുന്നു.
Snb + had + V3 + Obj

Future Perfect - ചെയ്തിട്ടുണ്ടാകും, ചെയ്യും
Snb + will have + V3 + Obj

Contracted forms

(a) I have nothing to tell you.
(b) I have told you that a thousand times!

Have you noticed that in the first sentence 'have' is pronounced as /hæv/; and in the second sentence, 'have' is pronounced as /v/.

In the first sentence 'have' is the main verb. Have is a helping or auxiliary verb in the second sentence. It helps to form the present perfect form of the verb 'tell'.

(a) I have never met him - /aɪv 'nevə 'metɪm/
(b) He has been away - /hi:z bɪn ə'weɪ/
(c) She had left early - /ʃi:d 'left 'ɜ:lɪ/
(d) I will let you know - /aɪl 'letjə 'nəʊ/
(e) That would be fine - /ðæt wʊd bɪ faɪn/
(f) What do you mean - /wɒdjə 'mi:n/
(g) Where does he live? - /weə dʌzɪ lɪv/
(h) What did you do - /wɒtdɪdjə du:/

Full form	Contracted form	Pronunciation
I am	I'm	/aɪm/
We are	We're	/wɪə/
You are	You're	/jʊə/
She is	She's	/ʃi:z/

It is	It's	/ɪts/
They are	They're	/ðeɪə/
There is	there's	/ðeəz/
I have	I've	/aɪv/
we have	we've	/wi:v/
he has	he's	/hi:z/
It has	It's	/ɪts/
She had	She'd	/ʃi:d/
I will	I'll	/aɪl/
you will	you'll	/ju:l/
She will	She'll	/ʃi:l/
It will	It'll	/ɪtl/
we would	we'd	/wi:d/
you would	you'd	/jʊd/
She would	She'd	/ʃi:d/
They would	They'd	/ðeɪd/

Intonation

Simply the rise and fall of the voice in speaking is called intonation.

Booking clerk : ↓Enquiries, Can I ↑help you?
passenger : What time does the right train for ↓Mumbai leave?

Booking clerk : The scheduled time is ↓9 P.m
passenger : Is it on ↑time tonight?

Booking clerk : ↓No. It's ↓two hours late. It's expected to leave ↓at 11.

Here,
the pitch of the voice falls/rises on ↓ enquiries

the pitch of the voice rises on ↑ help you?

What time does the right train for ↓ Mumbai leave?
The scheduled time is ↓ 9 P.m.
Is it on ↑ time tonight?

↓No. It's ↓ two hours late. It's expected to leave ↓ at 11.

When the pitch of the voice falls we call it the falling tone. when the pitch of the voice rises we call it the rising tone. we mark the falling tone with a downward arrow ↓ before the syllable on which

the pitch of the voice falls, and the rising tone with an upward arrow ↗ before the syllable at which the pitch of the voice rises.

Functions of intonation

ⓐ It's ↘ raining.
ⓑ Get me some ↘ water.
ⓒ Who's ↘ shouting?

These are three examples of the use of the falling tone. You would have noticed that the first is a definite remark, the second is an order and the third a wh-question (Seeking information). They show three typical functions of the falling tone.

ⓐ What's the ↘ hurry?
ⓑ The girls have ↘ left
ⓒ The box was ↘ empty
ⓓ Report him ↘ immediately
ⓔ When are we ↘ leaving.

ⓐ Are you ↗ ready?
ⓑ won't you ↗ come in?
ⓒ Don't go a ↗ way!
ⓓ Why are you ↗ crying?
ⓔ Be ↗ careful!
ⓕ I'm ↗ sorry.

The rising tone is used in yes-no questions (mostly used to confirm something), polite commands, questions showing concern, apologies etc.

Awareness of different accents

English is spoken as the mother tongue and as the second language in many part of the world though the english spoken in different countries is not very different in grammar, of course with a bit in pronunciation. While watching television & listening to the radio, we come across a variety of pronunciations British, American, etc. It's useful and necessary to understand these varieties.

In this topic we study two major varieties of pronunciation, British and American, and discuss a few major differences between them.

The way English is spoken in one region of country varies, sometimes slightly and sometimes greatly from the way it is spoken in another region of the country. But one type of pronunciation has come to be regarded as 'standard'. It is spoken by most of the news presenters on BBC TV and Radio. It is this type of pronunciation that people have in mind when they talk about British English pronunciation.

Regional variations in pronunciation are also very marked in the US. Apart the type of pronunciation that most newsreaders on the national television and radio networks use in the US is considered to be 'standard'.

British /ɑ:/ and American /æ/

Officer: What's your nationality, young man?.
Boy: I'm half American and half British.

In this Conversation, the Boy was saying he was /hɑ:f/ British and /hæf/ American. This is one of the most noticeable differences between British and American pronunciation. In a large number of words, when British English uses the /ɑ:/ sound, American English uses the /æ/ sound.

Eg:

Word	British English	American English
ask	/ɑ:sk/	/æsk/
bath	/bɑ:θ/	/bæθ/
Castle	/kɑ:sl/	/kæsl/
Dance	/dɑ:ns/	/dæns/
Fast	/fɑ:st/	/fæst/

British /ɒ/ and American /ɑ:/

(a) Conduct - /kɒndʌkt/ /kɑ:ndʌkt/
(b) Confidence - /kɒnfɪdəns/ /kɑ:nfɪdəns/
(c) Doctor - /dɒktə/ /dɑ:ktə/
(d) Politics - /pɒlɪtɪks/ /pɑ:lɪtɪks/

There are a large number of words in which British English uses the sound /ɒ/ on the first syllable, while American English uses the sound /ɑ:/.

British /njʊ:z/ and American /nu:z/

The word news is pronunced /njʊ:z/ with a /j/ sound before /ʊ:/ in British English. It is said as /nʊ:z/ without the /j/ sound in American English. There are several examples like this.

British /raɪtə/ and American /raɪdər/

In American English, the letter t is often pronounced /d/ when it comes between two vowel sounds. The word writer, said as /raɪtə/ in British English, may sound like /raɪdər/ in American Pronunciation. The /d/ sound is an approximation of the sound produced in American English. The actual sound is represented as /ɾ/ in standard dictionaries. This may not be a major difference Between

the two varieties of pronunciation, but it is necessary to recognize the right word while listening to American English.

Eg: On British, This is a physics la'boratəy
/lə'bɒrətri/

On American, This is a physics laboratoiay
/læbrətɔ:ri/

The advertisement /ədvɜ:tismənt/
The advertisment /ædvətaizmənt/

Such differences in stress are not many but it is necessary to be aware of them.

gional accents

of us start learning English several years we have been using our mother tongue naturally uch habits formed in the mother tongue influence y we speak English. This has resulted in 'regional' varieties of spoken english. ing on the speakers mother tongues. It takes able effort to correct these accents.

In most of our languages, words are

Spoken as they are written. But in English, as you know, pronunciation does not closely follow spelling. This leads to several difficulties when we speak English. for eg: a word like butter is written with a double 't' but there is only one /t/ sound in pronunciation: /bʌtəɔ/ and not /bʌttər/. Similarly filling is said as /filiŋ/ and not as /fillinŋ/. Consonant sounds are, generally speaking, not doubled in English while it is common in our mother tongue.

Eg: Rubber /rʌbəl/, written ~~write~~ /ritn/
immediate /imi:diət/, funny /fʌni/
Silly /sili/ etc..

How to remedy your defects

① Record a stretch of your speech, play it back and listen to it carefully for any features we have discussed above.

② You can listen to people of your region speaking English and identify the features that can cause confusion to listeners from other regions.

③ Ask your friend to tell you honestly the defect they find in your speaking.

④ Ask your teacher for feed back.

⑤ The best way to remedy the defects in your spee is to listen as much as possible to good models o speech and imitate them.

⑥ Use standard dictionaries such as Cambridge advanced learner's dictionaries and other good diction

15/1/23

① ഒരുപോലെ മറുപടി - Tit for tat
eg: Her reply was tit for tat

② What is the Ordinal status of Droupadi Murmu among the presidents of India ?

③ What is the Chronological Order of Droupadi Murmu among the presidents of India ?

④ A million dollar question - ഒരുപാട് പ്രാധാന്യമുള്ള ചോദ്യം.
eg: The million dollar question was are you honest ?

⑤ To make ends Meet - കഷ്ടപ്പെട്ട് ജീവിക്കുന്നു.
Father works hard to make ends meet.

⑥ There, There - സമാധാനിപ്പിക്കുന്നു.
eg: Hey, there there, don't cry
There there, just relax.

⑦ Take Care Of - പരിപാലിക്കുക
eg: My mother will take Care of me
They can take Care of themselves

⑧ Look After
eg: My mother will look after me
They can look after themselves

(9) Must - നിർബന്ധമായും ചെയ്യണം എന്ന അർത്ഥം, ഒഴിച്ചുകൂടാൻ പറ്റാത്ത
eg: Neenu Must obey the traffic rules while driving

Should - നിർദ്ദേശം, നിർദ്ദേശം
eg we should Speak English to improve fluency.

(10) Has Have - ഉണ്ട് (V3)
eg Aswanth has written an exam last week.

Had - ഉണ്ടായിരുന്നു (V3)
eg: Shivanand had bought an iphone last week.

Burn the mid night oil - രാത്രിയിലെ ഉറക്കമൊഴിച്ചിരുന്ന് പഠിക്കുന്നതും വലുതാക്കുക
eg: Anandu was burning the midnight oil for his final sem project.

Under the weather - സുഖമില്ല, തളർന്നിരിക്കുന്നു
eg: Aswin was a little under the weather last week.

need - ആവശ്യമുണ്ട്/ആവശ്യമാണ്
eg I need water to live
I need a ticket to travel.

want - just To improve our lives
eg: I want a new dress for the party

(15) Pass time
eg: listening to music is a pass time for me

(16) Host - നടത്തിക്കൊണ്ടുപോകുക, സംഘടിപ്പിക്കുക.
eg: Who will host the next world cup football

(17) Guest - അതിഥി
eg I have some guests today

(18) Have to - ചെയ്തിരിക്കണം എന്നോ ചെയ്യേണ്ടതാണ്
eg I have to attend the meeting (V1)

(19) Has to - ചെയ്തിരിക്കണം എന്നോ ചെയ്യേണ്ടതാണ്
eg: She has to look after the kid

(20) Had to - ചെയ്തിരുന്നു/ചെയ്യേണ്ടിയിരുന്നു/ചെയ്തിരിക്കണം/ചെയ്യേണ്ടതാണ്
eg: I had to write the exam
I had to do it before (V3)

106 Dubious (Adjuctive) - സംശയമുള്ള/ സംശയാസ്പദമായ.

107 Dig on - (Direct attack on something is called)

108 Pacify (Verb) - ആശ്വസിപ്പിക്കുക/ സമാധാനപ്പെടുത്തുക/ ശാന്തിപ്പെടുത്തുക.

109 Ping - Directly call me through electronic platform Please
Eg: Ping me Personally.

110 Captivate - ആകർഷിക്കുക

111 Stellar - നക്ഷത്രം പോലെയിരിക്കുന്ന/ Related to stars.

112 Nap - ചെറുമയക്കം

113 Preface - അവതാരിക

114 Compiling - സമാഹരിക്കുക

115 Monk - സന്യാസി

116 Distill - വാറ്റുക/ സത്തെടുക്കുക

117 Invaluable - വിലമതിക്കാനാകാത്ത

118 Manifest - പ്രകടമായ/ തെളിഞ്ഞ/ വ്യക്തമായ

119 Privilage - പ്രത്യേകാവകാശം/ പ്രത്യേകാനുകൂല്യം

120 Legacy - പാരമ്പര്യം/ വൈഭവം

121 Applaud - അഭിനന്ദിക്കുക/ പ്രശംസിക്കുക

122 Retain/ Detain - നിലനിർത്തുക/ പിടിച്ചുവയ്ക്കുക

123 At a pinch - അടുത്തൈക്ക് വെച്ച് പോലത്

124 Feast - അഭ്യാസം/ അസാധാരണ കൃത്യം/ അത്ഭുതവിദ്യ

125 Ironically - പരിഹാസരൂപേണ

126 Compassion - അനുകമ്പ/ കരുണ

127 Worthwhile - സമയം ചെലവഴിക്കുന്നതായ/ അനുകൂലമായ

128 Toll - ചുങ്കം

129 Subway - അടിപാത

130 Tithing - പത്തിൽ ഒരു ഭാഗം/ പത്തിലൊന്നാം

131 Delight - സന്തോഷം

132 Vivid - സജീവമായ

134 As time went on - സമയം കടന്ന് പോയി

135 Intensely - ശക്തമായി

136 Complied - സ്വീകരിക്കുക

137 Stark - തീവ്രമായ/ ശക്തമായ

138 Conjured - ഉത്തമമായ പ്രയോഗിക്കുക.

139 Incredible - അവിശ്വസനീയം

140 Wiser - ജ്ഞാനി

141 Enlightened - പരിജ്ഞാനമുള്ള

Mere - വെറും
Savor - സ്വാദാസ്വദിക്കുക / ഉ[illegible]
Blips - kind of sound
Float - [illegible]
Stream - പുഴ/ അരുവി
Pursue - പിന്തുടരുക
148 Subordinate - കീഴിലുള്ള
149 Harp - വീണ

150 Fewer - കുറവായ
151 Inflation - ഉയർച്ച/ വർധന
152 Leverage - [illegible]

Vow - പ്രതിജ്ഞ/ ശപഥം
Fuel - ഇന്ധനം/ ഇന്ധനം നിറയ്ക്കൽ
Preaching - മതപ്രചാരണം നടത്തൽ
Broom - ചൂൽ/ അടിച്ചുവാരുക

Dwell - താമസിക്കുക/ പാർക്കുക
Fortune - ഭാഗ്യം / ഐശ്വര്യം
Adversity - കഷ്ടകാലം/ വിപത്ത്
Bravery - ധീരത/ സാഹസം
Frontiers - അതിർത്തി
Mediocrity - സാമാന്യത്വം / ഇടത്തരമായത്
Sagely - ജ്ഞാനിയായ
Noble - കുലീനം
Cowardly - ഭീരുവായ / ധൈര്യമില്ലാത്ത

177 Setbacks - പുരോഗതിയ്ക്ക് തടസ്സമാകുന്ന
178 Perhaps - ഒരുപക്ഷേ
179 Anticipate - പ്രതീക്ഷിക്കുക/ മുൻകൂട്ടികാണുക
180 Profound - അഗാധമായ/ [illegible]
181 Wisdom - അറിവ്/ വിവേകം/ ജ്ഞാനം/ ബുദ്ധി
182 Aside - മാറ്റി/ [illegible]
183 Sanctuary - [illegible]

184 Replenish - വീണ്ടും നിറയ്ക്കുക
185 Ritual - [illegible]
186 Contemplation - ധ്യാനം/ [illegible]

187 Forged - നിർമ്മിച്ച/ കെട്ടിച്ചമച്ച/ ഉണ്ടാക്കിയ
188 Precision - കൃത്യത/ സൂക്ഷ്മത
189 Mastery - [illegible]
190 Clamor - [illegible]
191 Negotiate - [illegible]

192 Delegated - [illegible]
193 Legacy - പാരമ്പര്യം/ പൈതൃകം
194 Destined - വിധിക്കപ്പെട്ട

195 Neglect - അവഗണിക്കുക
196 Pursuits - ഉദ്യമങ്ങൾ

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Tremendous - അതിഗംഭീരമായ
Astonished - അത്ഭുതപ്പെടുത്തുക
Elite - ശ്രേഷ്ഠമായ
Revitalize - പുനരുജ്ജീവിപ്പിക്കുക
Solitary - ഒറ്റയ്ക്ക്
Drummer - ചെണ്ടക്കാരൻ
Litigation - വ്യവഹാരം/അന്യായം
Trappings - വേഷഭൂഷകൾ
Enormous - ഭീമമായ/ബൃഹത്തായ
Profound - ഗാഢമായ/പരമമായ/അഗാധമായ
Fascinate - ആകർഷിക്കുക/രസിപ്പിക്കുക
Serene - പ്രഭയുള്ള/ശാന്തമായ
Tranquil - കലങ്ങാത്ത/ശാന്തമായ
Heed - ശ്രദ്ധ/ഗൗനം/കരുതൽ/വകവയ്ക്കുക

Flooded - വെള്ളപ്പൊക്കം/ധാരാളമായി വരിക
Crazed - ഉന്മത്തനായ
Wile - തന്ത്രങ്ങൾ
Pyre - ചിത
Strikingly - ആകർഷകമായി/വിസ്മയിപ്പിക്കുന്നതായി
Sinking - താണ് പോകുന്ന/മുങ്ങി പോകുന്ന
Brood - അടയിരിക്കുക/ആലോചിച്ചിരിക്കുക
Wallow - ചെളിയിൽ കിടന്നുരുളുക

Coop - കൂട്
ut - പുറം തോട്
Intact - കേടുപറ്റാത്ത

DD/MM/YYYY
S M T W T F S

222 Pile - കൂട്ടം/കൂമ്പാരം
223 Disguise - വേഷം/വേഷപ്രച്ഛന്നം
224 Beneath - താഴെ/കീഴിൽ/അടിയിൽ

225 Deteriorate -
226 Perspiration - വിയർപ്പ്
227 Attribute - ലക്ഷണം/ഗുണം/ധർമം
228 Obsession - ബാധ/പിടി
229 Dread - ഭയാനകമായ
230 Affliction - ദുഃഖങ്ങൾ/ക്ലേശം
231 Amply - പൂർണ്ണമായ/ധാരാളമായ
232 Impoverish - ക്ഷീണിപ്പിക്കുക/ദരിദ്രമാക്കുക
233 Errand - നിയോഗം/ദൗത്യം/നിയോഗയാത്ര
234 Amid - ഇടയിൽ
235 Relentless - ദയയില്ലാത്ത/ശമനമില്ലാത്ത
236 Yield - ഉണ്ടാക്കുക
237 Lofty - ഉന്നതമായ
238 Serene - പ്രഭയുള്ള/ശാന്തമായ
239 Trivial - നിസ്സാരമായ/ബാലിശമായ
240 Benign - ദയയുള്ള/കരുണയുള്ള
241 Solitude - ഏകാന്തം
242 Carved - കൊത്തുപണികളുള്ള
243 Chunk - കട്ടി
244 Commodity - ചരക്ക്/ഉൽപന്നം
245 Awakend - ഉണർത്തപ്പെട്ട
246 Aground - കരയ്ക്കടുത്ത
247 Neglected - അവഗണിക്കപ്പെട്ട
248 Pervades - നിറഞ്ഞ് നിൽക്കുന്നത്.

249 Quest - അന്വേഷണം/ദൗത്യം

250 Jot - കുറിച്ചിടുക/കുറിച്ച് വയ്ക്കുക

251 Admirable - അഭിനന്ദനീയം/പ്രശംസനീയം

252 Foster - സംരക്ഷിക്കുക/ലാളിക്കുക

253 Traits - സ്വഭാവങ്ങൾ/ഗുണങ്ങൾ

253 optimistic -

254 Pesimist -

256 Scribble -

257 Sane -

258 Insane -

INTRODUCTORY DIALOGUE

(ആമുഖ സംഭാഷണം)

GREETINGS

Good Morning	: രാവിലെ മാത്രം
Good Afternoon	: ഉച്ചമുതൽ വൈകുന്നേരം വരെ
Good Evening	: വൈകുന്നേരം മുതൽ ബെഡ് ടൈം വരെ
Good Night	: രാത്രിയിൽ പിരിയുമ്പോൾ

സമയം ചോദിക്കൽ

What is the time? What time is it?	സമയമെന്തായി
It is 10 o'clock.	സമയം പത്തായി
It is 5 to 10.	സമയം 9.55
It is 10 past 10	സമയം 10.10
It is a quarter to 10	സമയം 9.45
It is quarter past 10	സമയം 10.15
It is half past 10	സമയം 10.30

A. FAMILY BACKGROUND (കുടുംബപശ്ചാത്തലം)

1. What is your name?
നിന്റെ പേരെന്താണ്
My name is Ancy.
എന്റെ പേര് ആൻസിയെന്നാണ്

2. How are you?
നിനക്ക് സുഖമാണോ?
I am very fine.
എനിക്ക് വളരെ സുഖമാണ്.

3. Where is your house?
നിന്റെ വീട് എവിടെയാണ്?
My house is in Thiruvananthapuram.
എന്റെ വീട് തിരുവനന്തപുരത്താണ്.

4. What is your father?
നിന്റെ അച്ഛനെന്താണ് ജോലി?
My father is an engineer.
എന്റെ അച്ഛൻ ഒരു എഞ്ചിനീയറാണ്.

5. What is your mother?
നിന്റെ അമ്മയ്ക്കെന്താണ് ജോലി?
My mother is a housewife.
എന്റെ അമ്മ ഒരു വീട്ടുകാര്യസ്ഥയാണ്.

6. How many are you at home?
നിങ്ങളുടെ വീട്ടിൽ എത്രപേരുണ്ട്?
We are six at home.
ഞങ്ങളുടെ വീട്ടിൽ ആറുപേരുണ്ട്.

7. How many brothers have you?
നിനക്ക് എത്ര സഹോദരന്മാരുണ്ട്?
I have two brothers.
എനിക്ക് രണ്ട് സഹോദരന്മാരുണ്ട്.

8. How many sisters have you?
നിനക്ക് എത്ര സഹോദരിമാരുണ്ട്?
I have a sister.
എനിക്ക് ഒരു സഹോദരിയുണ്ട്.

9. How many elder brothers have you?
നിനക്കെത്ര ചേട്ടന്മാരുണ്ട്?
I have no elder brothers.
എനിക്ക് ചേട്ടന്മാരില്ല.

10. How many younger brothers have you?
നിനക്ക് എത്ര അനുജന്മാരുണ്ട്?
I have two younger brothers.
എനിക്ക് രണ്ട് അനുജന്മാർ ഉണ്ട്.

11. How many elder sisters have you?
നിനക്ക് എത്ര ചേച്ചിമാരുണ്ട്

I have an elder sister.
എനിക്ക് ഒരു ചേച്ചിയുണ്ട്.

12. How many younger sisters have you?
നിനക്കെത്ര അനുജത്തിമാരുണ്ട്.
I have no younger sisters.
എനിക്ക് അനുജത്തിമാരില്ല.

13. How old are you?
നിനക്കെത്ര വയസുണ്ട്?
I am 20 years old.
എനിക്ക് 20 വയസുണ്ട്.

14. How old is your father?
നിന്റെ അച്ഛനെത്ര വയസുണ്ട്?
My father is 56 years old.
എന്റെ അച്ഛന് 56 വയസുണ്ട്.

15. How old is your mother?
നിന്റെ അമ്മയ്ക്കെത്ര വയസുണ്ട്?
My mother is 54 years old.
എന്റെ അമ്മയ്ക്ക് 54 വയസുണ്ട്.

B. Daily Routine (ദിനചര്യ)

1. When do you get up normally?
നീ സാധാരണയായി എപ്പോഴാണ് ഉണരുന്നത്?
I get up at 5.30 in the morning.
ഞാൻ രാവിലെ 5.30ന് ഉണരുന്നു.

2. When do you sleep normally?
നീ എപ്പോഴാണ് സാധാരണയായി ഉറങ്ങുന്നത്?
I sleep at 10 o' clock normally.
ഞാൻ പത്തുമണിക്ക് ഉറങ്ങുന്നു.

3. When do you have your breakfast?
നീ എപ്പോഴാണ് പ്രഭാതഭക്ഷണം കഴിക്കുന്നത്?
I have my breakfast at 10 o' clock in the morning.
ഞാൻ രാവിലെ പത്തുമണിക്ക് പ്രഭാതഭക്ഷണം കഴിക്കുന്നു.

4. When do you have your lunch?
നീ എപ്പോഴാണ് ഉച്ചഭക്ഷണം കഴിക്കുന്നത്?
I have my lunch at 12.30 p.m.
ഞാൻ 12.30ന് ഉച്ചഭക്ഷണം കഴിക്കുന്നു.

5. When do you have your tea?
നീ എപ്പോഴാണ് ചായ കുടിക്കുന്നത്?

SECTION - I

THE BASICS OF GRAMMAR

SECTION - I

THE BASICS OF GRAMMAR

Lesson 1

NOUN AND PRONOUN

1. NOUN (നാമം)

ഒരു വ്യക്തിയുടേയോ, സ്ഥലത്തിന്റെയോ, വസ്തുവിന്റെയോ പേരാണ്. **Noun.**

Examples:

Rajeev, Thiruvananthapuram, Mango

2. PRONOUN (സർവ്വനാമം)

ഒരു വ്യക്തിയുടെയോ, സ്ഥലത്തിന്റെയോ, വസ്തുവിന്റെയോ പേരിന് പകരം ഉപയോഗിക്കുന്ന വാക്കുകൾ സർവ്വ നാമങ്ങളാണ്

Examples:

I, We, You, He, She, It, They

1.	I	ഞാൻ/എനിക്ക്
	Me	എനിക്ക്/എന്നെ
	My	എന്റെ/എന്റെ
	Mine	എന്റേത്

4.	We	ഞങ്ങൾ/ഞങ്ങൾക്ക്
	Our	ഞങ്ങളുടെ/നമ്മുടെ
	Ours	ഞങ്ങളുടേത്
	Us	ഞങ്ങൾക്ക്

2.	You	താങ്കൾ/നീ/നിങ്ങൾ/നിനക്ക്
	Your	നിന്റെ/നിങ്ങളുടെ
	Yours	നിന്റേത്

5.	They	അവർ/അവ/അവർക്ക്
	Their	അവരുടെ/അവയുടെ
	Them	അവർക്ക്/അവയ്ക്ക്
	Theirs	അവരുടേത്/അവയുടേത്

3.	She	അവൾ/അവൾക്ക്
	Her	അവളുടെ/അവൾക്ക്
	Hers	അവളുടേത്

6.	He	അവൻ/അവന്
	His	അവന്റെ
	Him	അവന്

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OPTIMIZATION TECHNIQUES: AN OVERVIEW FOR FORMULATION DEVELOPMENT

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ABSTRACT

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. Quality refers to product free of contamination and delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests "QbD" assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. "Hence QbD relate to Product Performance".

Key words: Quality of the pharmaceutical product, Quality by Design, Contamination.

INTRODUCTION

In Pharmacy word "optimization" is found in the literature referring to any study of formula. In development projects pharmacist generally experiments by a series of logical steps, carefully controlling the variables and changing one at a time until satisfactory results are obtained. This is how the optimization done in pharmaceutical industry.

Optimization is defined as follows: "Choosing the best element from some set of available alternatives". It is the process of finding the best way of using the existing resources while taking in to the account of all the factors that influences decisions in any experiment. The objective of designing quality formulation is achieved by various Optimization techniques like DoE (Design of Experiment).

The term FbD (Formulation by Design) & QbD (Quality by Design) indicates that quality in the product can be built by using various techniques of DOE (Design of Experiment).

This FbD has replaced the OVAT (one variable at a time) strategy for Optimization completely [1].

Quality by Design (Qb D)

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance [2].

Application of QbD in Pharmaceutical Industry

Quality refers to product free of contamination and delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests "QbD" assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. "Hence QbD relate to Product Performance".

Benefits for Industry

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.
- Provides opportunities for more flexible regulatory approaches.
- Manufacturing changes within the approved design space without further regulatory review.

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- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.

DOE (Design of Experiment)

It is a mathematical tool for systematically planning and conducting scientific studies that change experimental variables together in order to determine their effect on a given response [3-8]. It makes controlled changes to input variables in order to gain maximum amounts of information on cause and effect relationships with a minimum sample size for optimizing the formulation

There are mainly four steps associated with DOE:

1. The design of the experiment (By using various models)
2. The collection of the data
3. The statistical analysis of the data and
4. The conclusions reached and recommendations made as a result of the experiment.

In Optimization Method various types of Model used from preliminary screening of factors to select their level and for finally study of their effect so it's depend upon the formulator to choose a suitable model for study and help in minimizing the experimenting time.

IMPORTANT TERMINOLOGY USED IN DOE FOR OPTIMIZATION

1. Variable

There are of two types of variables

Independent variables or primary variables

Formulations and process variables directly under control of the formulator. These includes ingredients

Dependent or secondary variables

These are the responses of the in progress material or the resulting drug delivery system. It is the result of independent variables

(b) Factor

It is Assigned and Independent variables, which affect the product or output of the process. It is an assigned quantitative and qualitatively like this

***Quantitative*:** Numerical factor assigned to it. Ex; Concentration- 1%, 2%, 3% etc.

***Qualitative*:** Which are not numerical. Ex; Polymer grade, humidity condition etc

(c) Level: Levels of a factor are the values or designations assigned to the factor

(d) Response surface: Response surface representing the relationship between the independent variables X_1 and X_2 and the dependent variable Y

(e) Run or trials: Experiments conducted according to the selected experimental design

(f) Screening: To sort out something from

(g) Contour Plot: Geometric illustration of a response obtained by plotting one independent variable against another, while holding the magnitude of response and other variables as constant

(h) Interaction: It gives the overall effect of two or more variables means lack of additivity of factor effects Ex: Combined effect of lubricant and glidant on hardness of the tablet

(i)MLRA (Multiple Linear Regression Analysis): The technique which express mathematically in form of quadratic equation the linear relationship between various independent variable and dependent variable (Response)

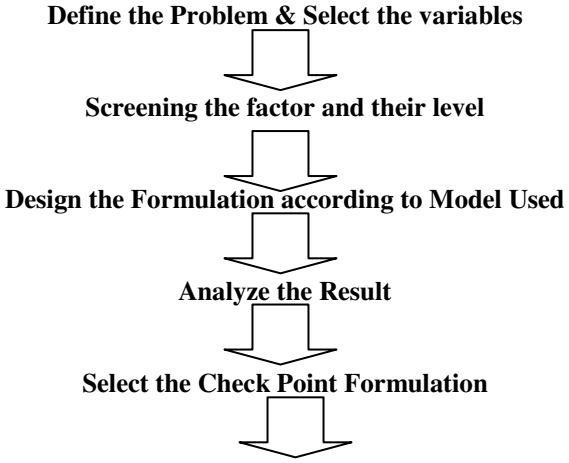
(j) Effect: It is the change in response caused by varying the levels and It gives the relationship between various factors & levels

(h) Response: It is an outcome of the experiment.

(i) Orthogonality: When effect is due to the main factor of interest and no interaction

(j) Confounding: Lack of Orthogonality is termed as confounding or aliasing

(k) Resolution: Measurement of degree of confounding



(Basic Flow Chart for using DOE and optimizing the formulation)

EXPERIMENTAL DESIGN

Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region, depends on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain, the point being defined by its co-ordinate (the value given to the variables) in the space [9-11].

TYPES OF EXPERIMENTAL DESIGN

There are various type of Experimental design methods are available out of which method we have to use depends upon the resources we have and what we want to study.

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Screening Designs are used for identify the important factor and their level which affect the Quality of Formulation. Screening Designs generally support only the linear responses.

Response Surface Designs are used when we required exact image of response, estimating interaction and even quadratic effects. Response surface designs generally support non linear and quadratic response and capable of detecting curvatures

Factorial Designs

Factorial designs (FDs) are very frequently used response surface designs. A factorial experiment is one in which all levels of a given factor are combined with all levels of every other factor in the experiment. These are generally based upon first-degree mathematical models. Full FDs involve studying the effect of all the factors *(k)* at various levels (x), including the interactions among them, with the total number of experiments being x^k. If the number of levels is the same for each factor in the optimization study, the FDs are said to be *symmetric,* whereas in cases of a different number of levels for different factors, FDs are termed *asymmetric."*

When we study three factors at two level $\mathbf{2^3}$ the total Number of run will be =08 &

When we study two factors at three level $\mathbf{3^2}$ the total Number of run will be =09

Fractional Factorial Design (FFD)

Fractional factorial design is generally used for screening of factor. This design has low resolution due to less number of run. Although these designs are economical in terms of number of experiments, the ability to distinguish some of the factor effects is partly sacrificed by reduction in the number of experiments.

Plackett-Burman Designs (Hadamard designs)

Plackett—Burman designs (PBD) are special two-level FFDs used generally for screening of factors. This design is generally used when we want to screen high number of factors (11-47) if we want to study the effect of 7 factors then we have to show four dummy factors. The interpretations of results in FFD, Plackett-Burman Designs & Taguchi design are drawn with the help of Pareto chart and Half normal plot.

Central Composite Design (Box-Wilson design)

For nonlinear responses requiring second-order models, central composite designs (CCDs) are the most frequently employed. A two-factor CCD is identical to a 3^2 FD with rectangular experimental domain at $\alpha = \pm 1$, On the other hand, the experimental domain is spherical in shape for $\alpha = \sqrt{2} = 1.414$.The CCD is quite popular in response surface optimization during pharmaceutical product development.

Box-Behnken Designs

A specially made design, the Box-Behnken design (BBD), requires only three levels for each facto -l, 0 and +1. It employing 15 experiments run with three factors at three levels. It is economical then CCD because t requires less number of Trial

Taguchi Design

Taguchi refers to experimental design as "off-line quality control" because it is a method of ensuring good performance in the development of products or processes." It is also used for screening of factors and it provides 8 experimental run for 7 factors.

Mixture Design

Mixture designs are used when the characteristics of the finished product (Drug delivery system) usually depend not so much on the quantity of each substance present but on their proportions. The sum total of the proportions of all the excipients is unity, and none of the fractions can be negative. Therefore, the levels of different components can be varied with the restriction that the sum total should not exceed one.

OPTIMIZATION OF IMPORTANT FACTORS

Model Development

A model is an expression defining the quantitative dependence of a response variable on the independent variables. Usually, it is a set of polynomials of a given order or Degree. From this polynomial equation we calculate the coefficient with the help of Principal of MLRA (Multiple Linear Regression Analysis). By the help of software we can also study here the effect of excipients, their interaction study, 3D Response plot, Contour Plot etc. In screening design with the help of half normal plot and Pareto chart we can find out easily the main factor and their level

From the models thus selected, optimization of one response or the simultaneous optimization of multiple responses needs to be optimized graphically, numerically and by using Brute force search technology.

(a) Graphical Optimization

Graphical optimization deals with selecting the best possible formulation out of a feasible factor space region. To do this, the desirable limits of response variables are set, and the factor levels are screened accordingly by the help of overlay plot.

(b) Brute-force search (Feasibility and Grid search)

Brute-force search technique is the simple and exhaustive search optimization technique. It checks each and every single point in the function space. Herein, the formulations that can be prepared by almost every possible combination of independent factors and screened for their response variables. Subsequently, the acceptable limits are

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set for these responses, and an exhaustive search is again conducted by further narrowing down the feasible region. The optimized formulation is searched from the final feasible space (termed as grid search), which fulfills the maximum criteria set during experimentation.

(c) Numerical Optimization

It deals with selecting the best possible formulation out of a suitable factor. To do this, the desirable limits of response variables are set, and the factor levels are displayed by the software. Other techniques used for optimizing multiple responses are canonical analysis, ANNs and mathematical optimization.

VALIDATION OF MODEL

The predicted optimal formulation (Check point) is prepared as per optimum factor level and the responses evaluated. On comparison of Results of Observed and predicted response conclusion will be drawn for model validation.

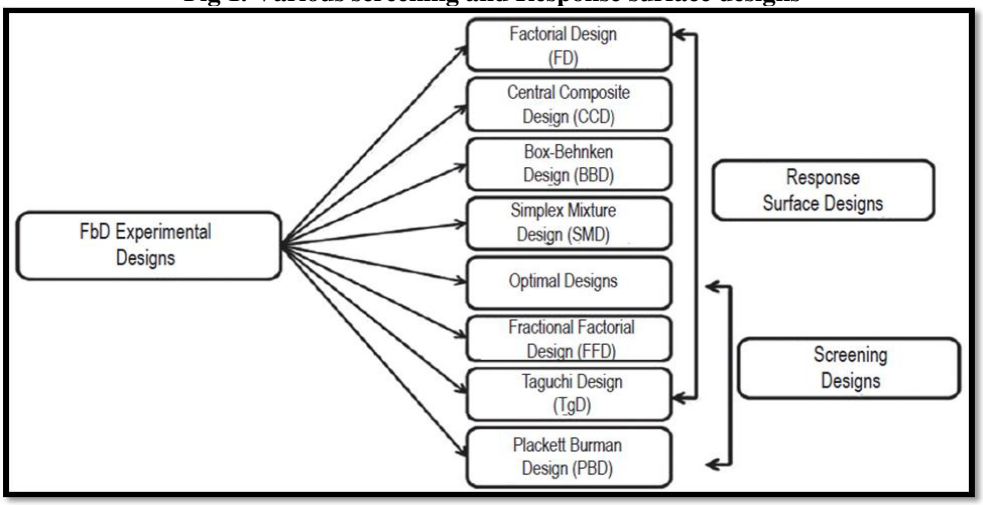
Software for Designs and Optimization

Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type.

Software's dedicated to experimental designs

- DESIGN EXPERT
- ECHIP
- MULTI-SIMPLEX
- NEMRODW
- Software for general statistical nature
- SAS
- MINITAB
- SYSTAT
- GRAPHPAD PRISM

Fig 1. Various screening and Response surface designs



CONCLUSION

The area of optimization is vary vast and its applications in all areas of pharmaceutical science. Different techniques have been used according to need. In this article, an overview of various techniques was given. Optimization techniques are help full in reducing the cost of product by minimizing the number of experimental trials during formulation development. It is very thirst area of Research now a day in every industry.

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Quality by Design (QbD) for Holistic Pharma Excellence and Regulatory Compliance

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Quality by Design (QbD) for Holistic Pharma Excellence and Regulatory Compliance

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The pharmaceutical industry has always demonstrated keen intent to produce drug products with enhanced quality for meeting the patient requirements. Consistent production of drug products with desired quality traits, however, has been an arduous challenge owing to prevalence of high degree of variability in active pharmaceutical ingredients, raw materials and/or processes. In an endeavor to address such crucial issues, the pharma houses have lately been undergoing transformation by adopting systematic approaches for developing drug products with enhanced quality, robustness and resource-economics. Recent impetus provided by key federal regulatory agencies (i.e., ICH and USFDA) through implementation of Quality by Design (QbD) guidance's has been the major driver in this context. QbD is verily a rational and orderly paradigm for developing drug products with pre-defined objectives to circumvent any quality crisis at the end, while emphasizing science and risk-based product and process understanding. Vital benefits of QbD encompass, enhanced knowledge sharing, improved time-to-reach-market, reduced consumer generic scepticism, reduced post-approval changes, and minimal product recalls. Considered as a QbD off-shoot, Formulation by Design (FbD) is a newer paradigm, particularly applicable to the development of drug formulations. Today, QbD applicability has permeated beyond the realm of formulation development to take into its ambit diverse pharmaceutical domains like drug substance manufacture, analytical method development, dissolution and bioequivalence testing, and stability testing. The current article, in a nutshell, endeavours to provide nuances of QbD philosophy, principles, methodology and applications during the entire product development life-cycle for accomplishing pharmaceutical excellence and regulatory compliance.

Keywords: Quality risk management (QRM), Formulation by design (FbD), Design space, Design of experiments (DoE), Experimental designs, Control strategy

Introduction

Since decades, the pharmaceuticalproducts have been rigorously regulated as these are meant to accomplish the desired therapeutic benefits to the patient community. Despite continuous innovations introduced by the pharma industry from time-to-time, there have been frequent encounters of recalls, rejects and failures ostensibly due to their quality and manufacturing standards not being upto the mark.The pivotal factor underlying such recurrent lapses to furnish the desired level of quality traits has been attributed to high degree of variability in drug substance(s), raw material(s), process(es), packaging material(s), etc.. Figure 1 portrays such multiple sources of variability during drug product development owing to variability in these sources.

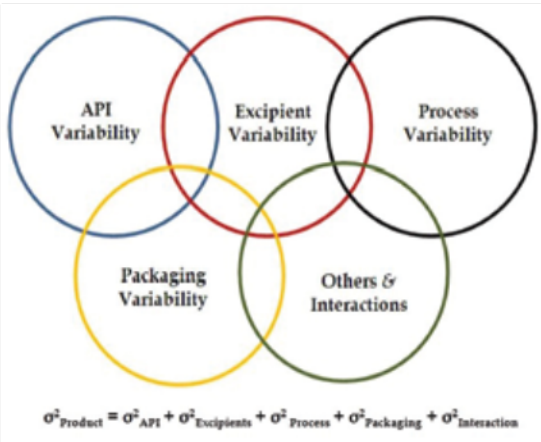

Figure 1: Sources of myriad variability during drug product development

Adoption of systematic approaches practically originated in the pharmaceutical industry following a thought provoking a article which appeared in The Wall Street Journal inSeptember 2002 that took the entire pharma world by storm. It was an eye-opener for the federal agencies too, as it stated, "although the pharmaceutical industry has a little secret even as it invents futuristic new drugs, yet its manufacturing standards lag far behind the potato chips and laundry soap makers".After escalating concern and criticism on the quality and reliability of pharmaceutical products, the ICH instituted a series of quality guidance's like Q8, Q9, Q10 and Q11,all emphasizing the adoption of systematic principles of Quality by Design (QbD) as its 21st century quality initiatives. Endorsement of such rational paradigms by USFDA, EMEA, MHRA, TGA, MCC, SFDA, Health Canada, and many other key global regulatory agencies is unequivocal testimony to their immense significance for all the potential stake holders, *viz.* patients, industrial scientists and regulators.With the growing pressure from their federal statutes, the pharmaceutical industry has been steadfastly reorienting its strategies and work policies. Regulatory agencies, today, emphasize only on QbD but not merely on "Quality by

Box 1: Phenomenal Benefits of implementing QbD approach during drug product development

Benefits of QbD implementation in product development
• Development of high quality drug products
• Thorough understanding of product(s) and process(es)
• Enhanced knowledge sharing
• Reduced consumer-generic skepticism
• Excellent returns on investment
• Improved time to reach market
• Dynamic control strategy leading to greater operational flexibility
• Limited product recalls and rejects
• Decreased post-approval changes
• Efficient regulatory oversight
• Regulatory filing based on science and mechanistic rationale
• Saves significant resources as testing is only real-time

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Testing (QbT)" or "Quality by Chance". Box 1 enlists the key differences between the traditional QbT and modern QbD approaches for developing drug products.

Verily, the QbD precepts were already in place before the introduction of federal guidelines coercing their implementation. Originated in early 1970's by J.M. Juran, an American engineer and quality analyst, the concept of "building quality into the system" was put into practice to develop the quality products and services initially by several technology-driven industries like, automobiles, telecommunications and aeronautics,. In fact, Juran believed that quality could be planned in the first place, thus avoiding any plausible quality crisis at the termination of the production cycle. Subsequently, this Juran'squality philosophy was adopted by healthcare industry in 1990's to produce the medical devices too. Introduction of these rational and systematic quality principles to most pharma industrial houses became apparent relatively quite late, i.e., in the twenty-first century only.

Based upon the Juran's quality philosophy, pharmaceutical QbD embarks upon systematic development of product(s) and process(es) with desired quality traits.As a patient-centric approach, the QbD philosophy primarily focuses on the safety of patients by developing drug products with improved and reproducible quality,coupled up with reduced manufacturing costs. Beginning with pre-defined objectives, QbD embarks upon enhanced knowledge and understanding on the products and processes based on the sound science and quality risk management.The diverse benefits of QbD approach, which could be harvested during drug product development,are enlisted in Box 2. Besides QbD, process analytical technology (PAT) tools have also garnered wide attention in the corner stone of FDA's quality initiativesfor design, control and analysis of quality of themanufacturing processes for their efficient monitoring and control.

Box 2: QbT and QbD grossly differ from each other

Quality by Testing (QbT)	Quality by Design (QbD)
• Current state of manufacturing • Relies on end-product testing • Testing outweighs the design • Quality attainment is never guaranteed • Doesn't get much along with Federal QbR • Time, effort and money consuming • Indecisiveness due to siloed conditions • Narrower operating ranges	• Desired state of manufacturing • End-product testing is for validation only • Testing balances with the design • Quality is always accomplished • Complements well with Federal QbR • Reduced expenditure of resources • Judicious planning using team approach • Wider operating ranges

Cardinal Principles of QbD:

The principal endeavor of QbD paradigm has been to accentuate the sound science-based and risk-based understanding of pharma manufacturing espousing rational and systematic approaches. QbD, verily, is a rational attitude of doing things right from the first step envisioning the nuances of entire procedural elements beforehand. The entire QbD exercise, therefore, aims at unraveling the scientific minutiae during systematic product development and manufacturing process(es), which would have hitherto remained as unearthed.

The first and the foremost task during QbD implementation, accordingly, is to prioritize the "vital few" among the possible "so many" variables affecting the particular pharma process or product. "Quality Risk Management (QRM)" is the key approach federally recommended and adopted for the purpose not only to provide holistic understanding of the patient risks associated during each stage of product development, but also to facilitate mitigation of risks. Another vital approach that helps the scientists during prioritization is the factor screening employing limited number of studies, planned and executed on the basis of simpler experimental designs.

One of the integral tools in the QbD armamentarium while developing optimized products and processes, nevertheless, has been "Design of Experiments (DoE)" employing apt usage of diverse experimental designs. Amidst a multitude of plausible interactions of the drug substance with a plethora of functional and non-functional excipients and processes, adoption of systematic approaches lead to evolution of the breakthrough systems with minimal expenditure of time, developmental effort and cost. With the objective of developing an impeccable products or processes, this task was earlier attempted through trial and error, supplemented with the previous knowledge, wisdom and experience of the formulator, termed as the short-gun approach or One Factor At a Time (OFAT) approach. Using this methodology, the solution of a specific problematic product or process characteristic cannot be achieved, and attainment of the true optimal solution was never guaranteed.However, the QbD-based approach usually provides systematic drug product development yielding "the best" solutions. Such approaches are far more advantageous, because they require fewer experiments to achieve an optimum formulation, reveal interaction among the drug-excipient-process, simulates the product performance and subsequent scale-up.

Figure 2: QbD leads to product and process understanding, and subsequent continual improvement

Besides QRM, factor screening and DoE, several other science-intensive tools like drug release kinetic modeling, IVIVC, etc.,and multivariate chemometric approaches like Principle Component analysis (PCA), Partial Least Squares Analysis (PLSA), etc., could be investigated to ameliorate our knowledge and understanding of the process and/or product at hand. Overall, Figure 2 illustrates the QbD-oriented development of drug product embarking upon the comprehensive understanding of the quality traits associated with a product(s) and process(es).

With the percolation of such systematized QbD-based paradigms, the domain of pharma ceutical product development has endowed a newer look towards drug formulation development and subsequent patient therapy. Albeit the benefits of QbD galore are lately being reapedin several other related pharma domains too, including indrug substance manufacturing, analytical development, etc., their major application still remains focused around the rational formulation development only.

QbD-Oriented Product Development: Formulation by Design (FbD)

Application of systematic DoE-intensive concept of QbD has widely been practiced in the industrial environs. Lately, this is being rationally amalgamated with quality risk management and sound science-based conception. Because of the much wider domain of QbD, a terser QbD-based precept, i.e., Formulation by Design (FbD), has been proposed by us, applicable specifically to the use of QbD in drug formulation development. The holistic FbD strategy revolves around five fundamental elements *viz.*

defining the Quality Target Product Profile (QTPP), identification of Critical Quality Attributes (CQAs), Critical Formulation Attributes (CFAs) and Critical Process Parameters (CPPs),selection of apt experimental designs for DoE-guided, precise definition of design and control spaces to embark upon theoptimum formulation, postulation of control strategy for continuous improvement. Figure 3 illustrates the five-step methodology for drug product development employing QbD-based approach.

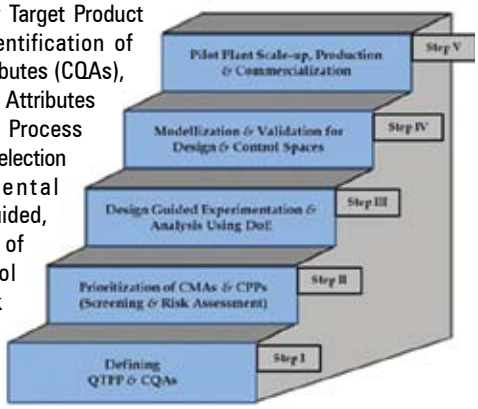

Figure 3: Five-step QbD ladder for product development

- Step I: Ascertaining Drug Product Objective(s)

The quality target product profile (QTPP) is a prospective summary of quality characteristics of the drug delivery product ideally achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product.During drug product development, QTPP is embarked through brain storming among the team members cutting across multiple disciplines in the industry. Critical Quality Attributes (CQAs) are the physical, chemical, biological or microbiological characteristic of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality.There are various types of CQAs associated with the drug products such as drug substance CQAs, excipients CQAs, packaging material CQAs, etc.The identification of prime CQAs from the QTPP is based on the severity of harm a patient may get plausibly owing to the product failure. Thus after defining the QTPP, the CQAs which pragmatically epitomize the objective(s), are earmarked for the purpose.

- Step II: Prioritizing Input Variables for Optimization

Material attributes (MAs) and process parameters (PPs) are considered as the independent input variables associated with a product and/or process, which directly influence the CQAs of the drug product. PPs can be of different types such as non-Critical Process Parameters (non-CPPs), Unclassified Process Parameters (UPPs) and Critical Process Parameters (CPPs). Ishikawa-Fish bone diagram are used for establishment of cause-effect relationship among the input variables affecting the quality traits of the drug product. Figure 4 illustrates a typical cause-effect diagram highlighting the plausible causes of product variability and their impact on drug product CQAs.

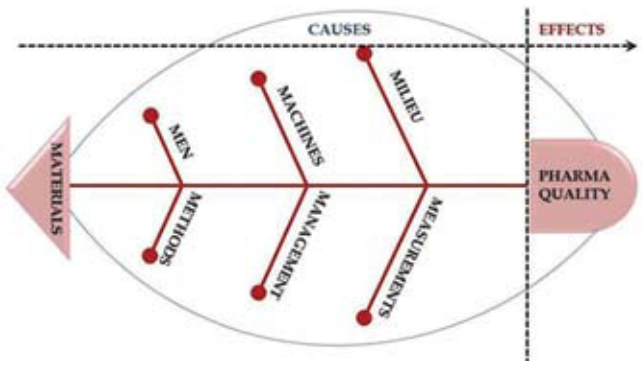

Figure 4: A typical Ishikawa fish bone diagram depicting plausible sources of variability

Prioritization exercise is carried out employing initial risk assessment and QRM techniques for identifying the "prominent few" input variables, termed as Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) from the "plausible so many". This process is popularly termed as factor screening. Comparison Matrix (CM), Risk Estimation Matrix (REM), Failure Mode Effect Analysis (FMEA) and Hazard Operability Analysis (HAZOP) are the examples of commonly employed risk assessment techniques. Using these techniques, various MAs and PPs are assigned with different risk levels *viz.* low, medium and high risk based on their severity and likelihood of occurrence. The moderate to high risk factors are chosen from patient perspectives through brain storming among the team members for judicious selection of CMAs. As a thumb rule, risk assessment using QRM is adopted along with DoE and factor screening using experimental designs during an archetypal QbD exercise (Figure 5).

Figure 5: Prioritization using QRM and factor screening is mandatory to identify CMAs and CPPs as a prelude to DoE optimization

Figure 6 portrays the flow layout of overall risk assessment plan employing risk assessment and risk management for identifying the potential CMAs employing a prototype REM model.

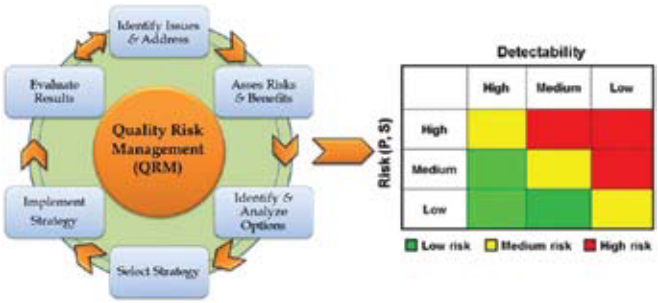

Figure 6: Layout of quality risk management (QRM) strategy employing risk estimation matrix

The low-resolution first-order experimental designs (e.g., fractional factorial, Plackett-Burman and Taguchi designs) are highly helpful for screening and factor influence studies. Before venturing into product or process optimization, prioritization of CMAs/CPPs using such QRM and/or screening is obligatory.

- Step III: Design-guided Experimentation & Analysis

Response surface methodology is considered as a pivotal part of the entire QbD exercise for optimizationof product and/or process variables discerned from the risk assessment and screening studies. The experimental designs help in mapping the responses on the basis of the studied objective(s), CQAs being explored, at high, medium or low levels of CMAs. Figure 7 diagrammatically enumerates the key experimental designs employed during QbD-based product development for response surface methodology and/or factor screening.Factorial, Box-Behnken, composite, optimal and mixture designs are the commonly used high resolution second-order designs employed for drug product optimization. Figure 8 delineates the diagrammatic representation of some of these designs using a cubic model depiction. Design matrix is a layout of experimental runs in matrix form generated by the chosen experimental design, to guide the drug delivery scientists. The drug formulations are experimentally prepared according to the design matrix and the chosen response variables are evaluated meticulously.

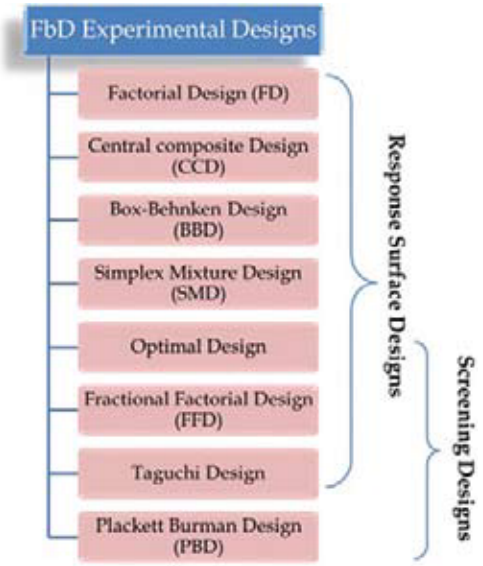

Figure 7: Key instances of experimental designs used during formulation by design (FbD)

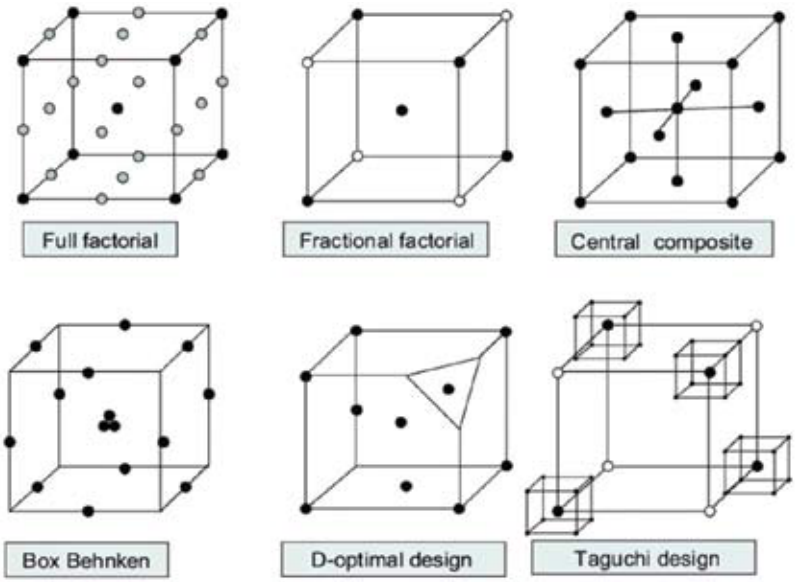

Figure 8: Pictographic representation of important experimental designs employed during FbD

• Step IV: Modelization & Validation of QbD Methodology

Modelization is carried out by selection of apt mathematical models like linear, quad-ratic and cubic models to generate the 2D and 3D-response surface to relate the response variables or CQAs with the input variables or CMAs/CPPs for identifying underlying interaction(s) among them. Multiple Linear Regression Analysis (MLRA), Partial Least Squares (PLS) analysisand Principal Component Analysis (PCA) are some of the key multivariate chemometric techniques employed for modelization to discern the factor-response relationship. Besides, the model diagnostic plots like perturbation charts, outlier plot, leverage plot, Cook's distance plot and Box-Cox plot are also helpful in unearthing the pertinent scientific minutiae and interactions among the CMAs too.The search for optimum solution is accomplished through numerical and graphical optimization techniques like desirability function, canonical analysis, artificial neural network, brute-force methodology and overlay plot. Subsequent to the optimum search, the optimized formulation is located in the design and control spaces.Design space is a multidimensional combination of input variables (i.e., CMAs/CPPs) and out variable (i.e., CQAs) to discern the optimal solution with assurance of quality. Figure 9 illustrates the interrelationship among various spaces like, explorable, knowledge, design and control spaces. Usually in industrial milieu, a narrower domain of control space is construed from the design space for further implicit and explicit studies.

Figure 9: Interplay of knowledge, design and control spaces

• Step V: QbD Validation, Scale-up and Production

Validation of the QbD methodology is a crucial step that forecasts about the prognostic ability of the polynomial models studied. Various product and process parameters are selected from the experimental domain and evaluated as per the standard operating conditions laid down for the desired product and process related conditions carried out earlier, commonly termed as checkpoints or confirmatory runs. The results obtained from these checkpoints are then compared with the predicted ones through linear correlation plots and the residual plots to check any typical pattern like ascending or descending lines, cycles, etc. To corroborate QbD performance, the product or process is scaled-up through pilot-plant, exhibit and production scale, in an industrial milieu to ensure the reproducibility and robustness. A holistic and versatile "control strategy" is meticulouslypostulated for "continuous improvement" in accomplishing better quality of the finished product.

Software Usage during QbD

The merits of QbD techniques are galore and their acceptability upbeat. Putting such rational approaches into practice, however, usually involves a great deal of mathematical and statistical intricacies. Today, with the availability of powerful and economical hardware and that of the comprehensive QbD software, the erstwhile computational hiccups have been greatly simplified and streamlined. Figure 10 enlist the select computer software available commercially for carrying out QbD studies in industrial milieu. Pertinent computer software available for DoE optimization include Design-Expert®,Minitab®, MODDE®,Unscrambler®, JMP®, Statistica®, etc., are at the rescue,which usually provide interface guide at every step during the entire product development cycle.Softwareproviding support for chemometric analysis through multivariate techniques like MNLRA, PCA, PLS, etc. encompass, MODDE®, Unscrambler®, SIMCA®, CODDESA®.For QRM execution using Fish-bone diagrams, REM and FMEA matrices during risk assessment studies, etc.,software like, Minitab®, Risk®, Statgraphics, FMEA-Pro, iGrafx, etc., can be made use of.

Figure 10: Select computer software used during QbD implementation for product and process optimization

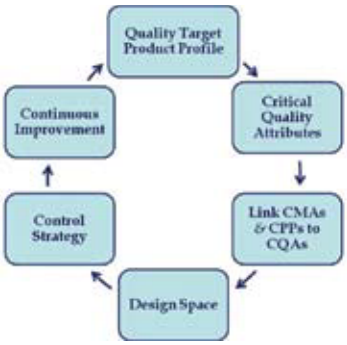

Figure 11: A bird's eye view of salient milestones during QbD implementation as per the federal requirements

For product development, in a nutshell, the fundamental elements that federal agencies anticipate from a QbD-oriented regulatory submission are represented as a sequential mandala, as in Figure 11.

QbD during Various Stages of Product Life-Span

In fact, the utility of versatile QbD approach is not only restricted to various stages of product development of small molecules as well as bigger biological macromolecules, but extends to the entire product lifespan. Appliance of QbD at various stages of product lifespan, starting from the early developmental phase to even after the post-approval commercial launch and post-marketing surveillance stage, is spelled out as:

Preclinical developmental phase

The ability to use prior knowledge from previous products, prior published or patent literature and prior experience is helpful in applying QbD during early stages of developing the lead molecule. Prior knowledge of patient needs helps in meeting the requirement of desired quality characteristicsin the new drug product.

Nonclinical and clinical phase

To meet the predefind specifications, the experiments condcted at preclinical and nonclinical stage are used to meet the requirements of the target product. This includes the in vitro and in vivo tests, depeding upon the type of product, feasibility experiments, toxicology tests or clinical study details. Under the ambit of QbD-based approach of product development, clinical studies help in providing thought-through information on the quality attributes of the product and help in microrefinment of the product and manufacturing process(es).

Scale-up phase

QbD tends to provide a great deal of understanding during scale-up phase. This allows to document changes and rationalizes during changeover from small pilot scale to the full-scale commercial manufacturing. Further, the information extracted at this stage is useful in designing the control strategy for continuous improvement.

Marketing approval phase

Submissions based on QbD provide more scientific information on the product, processes and change controls employed during optimization. This helps in improving the quality of submissions and ultimately provides regulatory flexibility for faster approval from the regulatory agencies.

QbD Applicationsin Various Other Pharma Sectors

Beyond any cynicism, QbD has been an inimitable quality-targeted approach for attaining excellence while developing efficacious, cost-efficacious, safe and robust drug products. Besides, it facilitates macroscopic and microscopic comprehension of products or processes, and helps in accomplishing federal compliance with phenomenal ease and economy, whether for generics or innovator's.

Today, a pharmaceutical scientist on industrial fronts has not only been deriving its stellar benefits during entire product development life-cycle, but beyond too. The other key domain where QbD principles are being used frequently used encompasses the analytical method development. In addition, QbD has slowly been percolating into several other interdisciplinary areas like API development, dissolution testing, manufacturing, bioequivalence studies and stability testing too. Figure 12 pictorially illustrates the application of strategic principles of QbD duringdiverse phases of drug product development cycle.

Figure 12: Omnipresence of QbD during the entire pharma product life cycle

Analytical QbD (AQbD)

AQbD, on the heels of QbD, endeavors for understanding the predefined analytical objectives.These comprise, Quality Target Method Profile (QTMP) of an analytical method,and identifying the Critical Method Variables (CMVs) affecting the Critical Analytical Attributes (CAAs)for attaining enhanced method performance, like high robustness, ruggedness and flexibility for continual improvement within the ambit of analytical design spac. Besides, AQbD helps in reducing and controlling the source of variability to gain in-process information for taking control decisions in a timely manner.This facilitates attaining flexibility in analysis of API and impurities in dosage forms, stability samples and biological samples and to go beyond traditional ICH procedure of method validation.Like FbD, the AQbD also embarks upon risk-assessment studies through REM/FMEA, andDoE-guided factor screening and optimization studiesfor improving the method performance. Instances of CMVs during AQbD optimization include mobile phase composition, flow rate, gradient time, column oven temperature, pH, while CAAs include peak area, retention time, theoretical plates, asymmetry factor and capacity factor.

QbD during drug substance development

Developing drug substances employing the systematic QbD-based paradigm has been recently popularized to accomplish the desired objective of producing drug substance with reduced variability, high purity and yield. ICH Q11 guidance, in this regard, provides detailed understanding of the key principles of manufacturing drug substance employing rational paradigms. As per the QbD approach, the quality target profile for drug substance are defined, which includes molecular, physiochemical and biological properties, pharmacokinetics, storage and packaging conditions, etc. The concentrations of reactants, solvents, initiators, stabilizers employed during synthesis of drug substance are mainly used as the CMAs, which are subsequently optimized for their impact on CQAs like, API particle size and size distribution, polymorphism, hygroscopicity, density, flow property, aqueous solubility, etc.

QbD in dissolution testing

As dissolution testing is primarily considered as one of the most important quality control test for preparing the release specification for any pharmaceutical dosage form, the QbD approach helps in optimizing the drug product composition for accomplishing analogous drug release profile to that of the reference listed product. Important examples of CQAs which determines the product quality include amount of drug release at specified time intervals, mean dissolution time, dissolution efficiency, release exponent, etc., whereas the concentration of polymers, disintegrants, type of medium are used as CMAs which tend to affect the dissolution profile of drug products.

QbD in bioequivalence testing

Implementation of QbD during bioequivalence study helps in optimizing the drug products (i.e., generics) in obtaining desired pharmacokinetic profile matched with that of the reference listed product. Important pharmacokinetic metric like, C_{max}, T_{max}, AUC, AUC_{0-t}, AUC_{∞}, are considered as the critical quality traits for optimizing the formulation variables like, concentration of release controlling polymer, coating composition, coating percentage, etc.

QbD in biologicals and herbals

Most often, QbD has been applied to the development of processes and products of small molecules only. Though quite disparate from each other, the biologicals and herbals both, on the other hand, are relatively more intricate, multi-component and heterogeneous systems which are not precisely defined, analyzed or characterized. Hence, scrupulous understanding of the relationships between process variables, and product CQAs is obligatory for such products. Several attempts have lately been made to apply chemometric multivariate tools and DoE to develop optimized processes yielding robust biosimilars, improved yield of production of proteins, enzyme, etc., and upgraded efficiency of herbal extraction procedures.

QbD in stability testing

QbD approach in stability testing furnishes better understanding of the product stability and shelf-life, information on degradation products, compatibility of container(s)/closure(s) with packaging materials. This helps in preparing the specifications related to safety, efficacy of finished product(s) with respect to the concentration of degradants and final qualifications of them for marketing approval.

QbD-based work at Panjab University: Evolution of a Revolution

The sojourn of implementing systematic approaches using DoE started at University Institute of Pharmaceutical Sciences (UIPS) at Panjab University way back in early 1990'ssomewhat quite intuitively, when the entire pharma world was banking on the traditional OFAT approach of developing the drug products. As the implementation of DoE invariably involved intricate algorithms and computations, availability of dedicated computer software was considered indispensable to take off. Requests for DoE software ex-gratis having been failed, the author, with the help of a scholar, wrote the DoE software in FORTRAN 90, christened as "FACTOP", containing proviso for factorial, composite and mixture designs. Since then, the adoption of systematic approaches has been a regular phenomenon at the Institute for developing novel and nanostructured DDS of diverse types employing diverse experimental designs and multivariate techniques. Over the period of time, incorporating newer QbD-oriented vistas such as QRM and chemometric tools, more than 70 papers have been published exclusively on QbD-enabled development with three comprehensive reviews as the most sought-after repertoire of information on FbD and DoE across the globe.

Table 1 and Table2 enlist the instances on application of QbD on drug delivery products and analytical method optimization, respectively, indicating thediverse type(s) of experimental design(s) employed as well.

Several hundreds of scientists have been trained on QbD-based concepts through onsite training seminars and Conference workshops. The collage in Fig. 13 portrays some of the logos of industrial houses with which industry-academia interactions have taken place primarily through training on QbD paradigms.

A number of highly prestigious recognitions, awards and accolades have poured exclusively in appreciation of the QbD-based work conducted at the Institute, as:

Table 1: A chronological account on the application of FbD methodology in the development of novel nanostructured drug delivery systems in our laboratories

Drug Delivery Systems	Drug	FbD Designs	Software	Year
Hydrophilic matrices	Diclofenac	FD	FACTOP	1997
	Captopril	FD	FACTOP	1998
	Verapamil HCl	CCD	FACTOP	2001
CRmicrospheres	Diltiazem HCl	FD	FACTOP	2002
Buccoadhesive tablets & films	Diltiazem HCl	FD	FACTOP	2002
	Rivastigmine HCl	PBD, CCD	Minitab	2012
Solid dispersions & Inclusion complexes	Flurbiprofen	FD	FACTOP	2002
	Meloxicam	CCD	Design Expert	2005
	Nimesulide	D-OD	Design Expert	2006
	Rofecoxib	CCD	Design Expert	2007
Flexible liposomes	Nimesulide	FD	Design Expert	2005
	Diclofenac	D-OD	Design Expert	2009
Liposomal gels	Clobetasol-propionate	CCD	Design Expert	2005
	Tamoxifen	TgD, FCCD	Design Expert	2005
Mucoadhesive tablets	Atenolol	CCD	Design Expert	2006
	Verapamil	CCD	Design Expert	2007
	Lamivudine	CCD	Design Expert	2007
Gastroretentive-floating-bioadhesive tablets	Trimetazidine HCl	CCD	Design Expert	2008
	Hydralazine HCl	CCD	Design Expert	2009
	Zidovudine	CCD	Design Expert	2012
	Lamivudine	FCCD	Design Expert	2012
	Rivastigmine	FCCD	Design Expert	2012
SNEDDS	Carvedilol	CCD	Design Expert	2008
	Raloxifene	D-OD	Design Expert	2009
	Simvastatin	CCD	Design Expert	2010
	Candesartan	MD	Design Expert	2010
	Lopinavir	TgD, D-OD	Design Expert	2013
	Darunavir	FFD, D-OD	Design Expert	2014
	Paclitaxel	TgD,FFD,D-OD	Design Expert	2014
Supersaturable SEDDS	Ezetimibe	PBD, CCD	Design Expert	2012
Solid SNEDDS	Carvedilol	CCD	Design Expert	2010
	Valsartan	FFD, CCD	Design Expert	2012
	Lovastatin	FCCD	Design Expert	2013
	Ezetimibe	TgD, D-OD	Design Expert	2014
Eutectic SNEDDS	Olmesartan	IV-OD	Minitab	2013
Transdermal gels	Tenoxicam	FD	FACTOP	2002
In situ gelling systems	Acyclovir	CCD	Design Expert	2010
Nasal microspheres	Lercanidipine HCl	CCD	Design Expert	2010
	Quercetin	CCD	Statgraphics	2012
SLNs	Etodolac	CCD	Design Expert	2011
	Quercetin	CCD	Design Expert	2011
	Methotrexate	FCCD	Design Expert	2014
	Darunavir	TgD, CCD	Design Expert	2014
NLCs	Isotretinoin	CCD	Design Expert	2011
	Lopinavir	PBD, BBD	Design Expert	2014

Drug Delivery Systems	Drug	FbD Designs	Software	Year
Nanoemul -somes	Dithranol	FCCD	Design Expert	2012
Nanoemulsions	Prilocaine	D-OD, FCCD	Design Expert	2014
*In Situ*gelling periodontal nanoparticles	Ofloxacin	CCD	Design Expert	2012
	Ornidazole	CCD	Design Expert	2012
	Moxifloxacin	TgD	Design Expert	2014
Phospholipid	Methotrexate	D-OD	Design Expert	2005
	Cyclosporine	CCD	Design Expert	2006
Oral mucosal vaccines	Diphtheria toxoid	BBD	Design Expert	2013
Nanobiolo-somes	Diphtheria toxoid	FCCD	Design Expert	2012
Ethosomes	Lidocaine & Prilocaine	FMEA, PBD, BBD	Design Expert	2014
Functionalized CNTs	Berberine	BBD	Design Expert	2014
Mixed Micelles	Tamoxifen	TgD, BBD	Design Expert	2014

BBD: Box-Behnken Design, CCD: Central Composite Design, CNTs: CarbanNanotubes, D-OD: D-Optimal Design, FCCD: Face Centered Cubic Design,FD: Factorial Design, HCl: Hydrochloride, MD: Mixture Design, NLCs: Nanostructured Lipid Carriers, PBD: Plackett-Burman Design, SLNs: Solid Lipid Nanoparticles, SNEDDS: Self Nano-emulsifying Drug Delivery Systems, TgD: Taguchi Design.

Table 2: An account on the application of Analytical quality by design methodology in our laboratories

Analytical Method	Drug	FbD Designs	Software	Year
RP-HPLC	Methotrexate	TD, BBD	Design Expert	2014
	Olmesartan-medoxomil	TD, FCCD	Design Expert	2014
RP-UPLC	Docetaxel	PBD, FCCD	Design Expert	2014

BBD: Box-Behnken Design, FCCD: Face Centered Cubic Design, HPLC: High performance liquid chromatography, PBD: Plackett Burman Design, RP: Reverse phase, TD: Taguchi Design, UPLC: Ultra pressure liquid chromatography.

Figure 13: Our liaison with various pharma industrial houses esp. to impart QbD-based training

- Pharma QbD Excellence Award 2012 by CPhI Asia Conferences, Ahmadabad.
- AAPS QbD & Product Performance Award 2012, Chicago, USA.
- AAPS QbD & Product Performance Award 2013, San Antonio, Texas, USA.
- OutstandingQbD Scientist Award 2014 by Select Bio, Mumbai, 2014.
- Pharma QbD Performance Award 2014 byM/s Stat-Ease Inc., Minneapolis, USA.

The unquenchable thirst and unflinchable quest for knowledge has still been continuing to reinforce our humble contribution in this domain of QbD so far….

EPILOGUE

Today, the federal agencies look for assurance of patient-centric quality "built-in" into the system, rather than through end-product testing. Notwithstanding the enormous utility of QbD-based philosophy in developing optimal drug products, it leads research mindsets to evolve "out-of-box" strategies too. As variability tends to exist at each and every stages of product development life cycle, QbD application needs to be omnipresent. Apt implementation of QbD paradigms, accordingly, would be pivotal in achieving a "win-win situation" for patients, drug industry and regulators. The practice of systematic QbD implementation for products has undoubtedly spiced up over the past a few decades, yet it is far from being adopted as a standard practice. Federal regulations for generic drug products are already in place. Several initiativesstill need to be undertaken to inculcate mundane use of diverse QbD paradigms in the holistic domain. Apart from these, the synergistic use of in-process PAT and RTRT tools in tandem with process engineering approaches like extensometry and chemometry,can also be helpful in ameliorating product and process understanding and enhancing the process capability for efficient manufacturing.With the growing acceptance of QbD paradigms, in a nutshell, it is rationally prophesized that soon these QbD philosophies will be required to be implemented to innovators, biosimilars, analytical development, API development and even beyond.

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A comprehensive review on quality by design (QbD) in pharmaceuticals

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Review Article

A Comprehensive Review on Quality by Design (QbD) in Pharmaceuticals

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ABSTRACT

Quality by Design (QbD) refers to a holistic approach towards drug development. Quality by design is a vital part of the modern approach to pharmaceutical quality. There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of quality by design. The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and illustrate how it can be used to ensure pharmaceutical quality. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include: Defining Quality target product profile, Identifying critical quality attributes, link the drug excipients attributes, establishing design space, control strategy, and product life cycle management. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. A new approach to drug development could increase efficiencies, provide regulatory support and flexibility, and offer important business benefits throughout the product's life cycle. This article explores the processes used in developing a market formulation and required supportive data, particularly in light of the industry's current movement toward submissions based on QbD. The work also facilitates the adoption and implementation of QbD. principles in the development of pharmaceutical industries. Successful implementation of QbD concepts requires cooperation across a multitude of company teams, from R&D to manufacturing to quality control and regulatory affairs. This is necessary to ensure that QbD concepts are incorporated not only when the first activities are initiated around a product's design but also during the design of the process used to make the product and other activities associated with a product's life cycle. The application of the concept of quality by design (QbD) presented in this paper aligns with the principles of ICH Q8, Q9 and Q10 guidelines.

Keywords: control strategy, critical material attributes, critical process parameters, design space, Quality by design.

INTRODUCTION

Quality by Design (QbD) was first described by Joseph M. Juran[1], and applied heavily, particularly in the automotive industry. The fundamental premise behind QbD is that quality can be "designed in" to processes through systematic implementation of an optimization strategy to establish a thorough understanding of the response of the system quality to given variables, and the use of control strategies to continuously ensure quality. The FDA has recently begun to advocate the QbD methodology for the pharmaceutical sector.[2]

In order to describe quality by design, we must first define what we mean by quality. In a 2004 paper, Janet Woodcock (Director for the Centre for Drug Evaluation and Research) defined pharmaceutical quality as a 'product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer'.[3]

'Quality in manufacturing is a measure of Excellence or a state of being free from defects, deficiencies, and significant variation'.

This explanation focuses on the QbD for generic drugs. The concept of QbD was mentioned in the ICH Q8 guidance, which states that "quality cannot be tested into products, i.e., quality should be built in by design". This paper discusses the pharmaceutical quality by design and describes how it can be used to ensure pharmaceutical quality with emphasis on solid oral dosage forms of small molecules. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs—and to comply with regulatory requirements to demonstrate that the drugs are safe and effective. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle. This article explores the processes used in developing a market formulation and requisite supportive data, particularly in light of the industry's current movement toward submissions based on quality by design (QbD). It outlines activities that should be performed early in the drug development process before initiating manufacturing and attempting market entry. The article identifies the type of data needed to address regulatory concerns and provides a pragmatic baseline for manufacturing facility requirements. Finally, it introduces new technologies that support the QbD approach. This paper describes a concise, coherent, and universal approach for determining criticality for parameters, material attributes, conditions, and quality attributes. The work also explains the risk based distinctions governing the assignment of criticality to provide consistency and facilitate the adoption and implementation of Quality by Design (QbD) principles in the development of pharmaceutical manufacturing processes. This paper describes an approach and technical process for

developing and implementing a Control Strategy, which is a planned set of controls, derived from current product and process understanding that assures process performance and product quality. Development of a Control Strategy requires a structured process, involving a multidisciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment. This paper concentrates on the techniques and principles involved in developing the early Control Strategy rather than the operational implementation of the strategy. This paper describes progress made by the Design Space within the Product Quality Lifecycle. Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions. The focus of this paper is on the technical elements of Design Space development.[4, 5]

QUALITY

"The degree to which a set of inherent properties of a product, system or process fulfils requirements" (ICH Q9)

"Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes."

Pharmaceutical Quality by Testing

Product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products.[6] Since a few tablets out of several million are tested, drug manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity, tablet hardness, etc; to ensure the outcome of in-process testing also meets the FDA approved in-process testing specifications. Manufacturers are also not permitted to make changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA. As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years. For example, in 2005 and 2006, the FDA Office of Generic Drugs received over 3,000 CMC supplements annually.[7-10] This combination of fixed manufacturing steps and extensive testing is what ensures quality under the traditional system. Limited characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance [11] .Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these debates are concentrated on acceptance limits or statistical aspects. FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products or they do not share this information with FDA reviewers. Under the traditional regulatory evaluation system, all products are treated equally without regard to the risk to the consumer.[12] This has the effect of placing too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. CMC review assessments of complex dosage forms (modified release products, topicals and transdermals) as well as narrow therapeutic index (NTI) drugs differ only marginally from those of simple dosage forms (many immediate release solid oral products). Further, all CMC information in applications are sometimes evaluated equally, without differentiation of criticality, resulting in the requirement of intensive resources for each application.

In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. The present regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Product specifications often are derived using test data from one or more batches (often not at production scale), and mechanistic understanding does not play a significant role in this process. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous "real time" assurance of quality.

Pharmaceutical Quality by Design

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management (*ICH Q8(R)*)

QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality. Thus, QbD requires an Understanding and controlling formulation and manufacturing process variables influence product quality.

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality.

ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." ICH Q6A emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."[13] Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control.[14] It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.[15] In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time.

Figure 1: Overview of QbD

Thus, some of the QbD elements may include,

- Define quality target product profile that describes the use, safety and efficacy of the product.
- Design and develop product and manufacturing processes.
- Identify critical quality attributes, process parameters, and sources of variability.
- Establish a control strategy for the entire process.
- Control manufacturing processes to produce consistent quality over time.

Under the QbD concept, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance. QbD requires an understanding how formulation and process variables influence product quality. These discussions have generally focused on the development of new drugs. Drawing on these discussions and some specific aspects of the development of generic products, a QbD development process may include & begin with a target product profile that describes the use, safety and efficacy of the product & Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development & Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation & Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile & Design a manufacturing process to produce a final product having these critical material attributes & identify the critical process parameters and raw material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding & establish a control strategy for the entire process that may include raw material controls, process controls and monitors, design spaces around individual or multiple unit operations, and final product tests. The control strategy should include expected changes in scale and can be guided by a risk assessment & continually monitor and update the process to assure consistent quality Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. The difference between QbD for NDA and ANDA products is most apparent at the first step of the process. For an NDA, the target product profile is under development while for the ANDA product the target product profile is well established by the labelling and clinical studies conducted to support the approval of the reference product Table 1.

Table 1: Current Vs QbD approach to pharmaceutical development

Conventional Product Development	QbD Approach (Ideal)
Quality assured by end product testing and inspection and mainly an empirical approach.	Quality built into product & process by design, based on scientific understanding and a systematic approach.
Data intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process" disallowing changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on formulation and process robustness – understanding and controlling variation

"Quality is built in by design, not tested in"

"Quality by design is about doing things consciously."

Key Aspects of Qbd

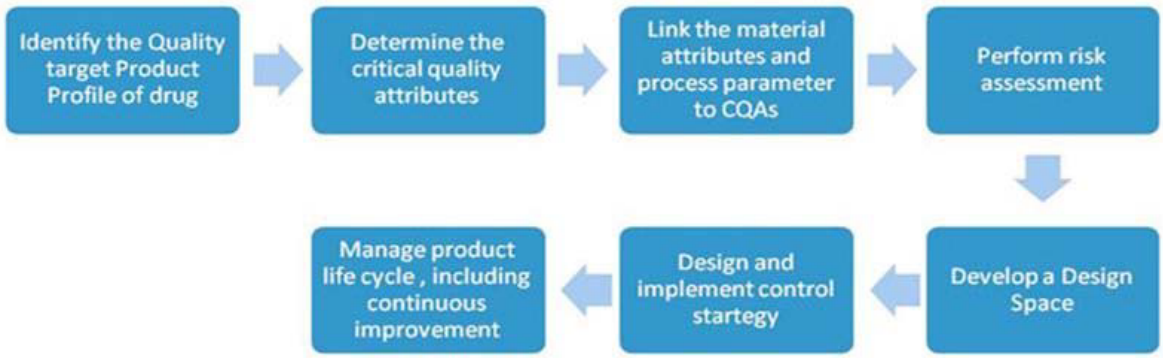

Figure 2: Flow diagram (Key Aspects of QbD)

TARGET PRODUCT PROFILE (TPP)

FDA published a recent guidance defining a Target Product Profile (TPP): "The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labelling and links drug development activities to specific concepts intended for inclusion in the drug labelling." When ICH Q8 says that pharmaceutical development should include "...identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration", the consideration of the intended usage and route of administration would be through the TPP.

The TPP is a patient and labelling centred concept, it can be thought of as the "user interface" of the drug product. Thus a generic version and its reference product would be expected to have the same TPP. A generic product may use a different formulation or design to implement the TPP. The characteristics and performance tests of a drug product would depended on the particular implementation and may differ between a generic and reference product.

For a new drug, changes to the TPP may require new safety or efficacy data.

For Reformulation, Changes to product characteristics or performance that result from a reformulation may not require that data.

Many aspects of the TPP determine the actions of formulation and process development scientists. It is the role of a pharmaceutical scientist to translate the qualitative TPP into what we define as the target product quality profile (QTPP) for further use in a quality by design process.

Identifying Quality Target Product Profile (Qtpp)

"Begin with the end in mind"

By Beginning with the end in the mind, the result of development is robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product.

The quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product.

The quality target product profile (QTPP) is a quantitative substitute for aspects of clinical safety and efficacy.

International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile.

Quality target product profile (QTPP) Includes, but not limited to:

- Dosage form
- Route of administration
- Strength
- Release or Delivery of the drug
- Pharmacokinetic characteristics

e.g., dissolution, aerodynamic performance

- Drug product quality characteristics for intended use e.g., sterility, purity.

Generic products would include bioequivalence to the RLD as part of the QTPP. The QTPP is not a specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. The QTPP should only include patient relevant product performance. For example, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size. Particle size would be a critical material attribute and thus included in the process description and control strategy. The QTPP should be performance based and not mechanism based.[16-17]

Drug Substance and Excipient Properties

Drug substance–physicochemical and biological properties in relation to product performance and manufacturability.

Excipients - concentration, characteristics and functionality in relation to product performance and manufacturability and functionality during shelf-life.

It is well recognized that excipients could be a major source of variability. Characterization and understanding of excipients' pharmaceutical properties depend on the function and utility of excipients. Drug-excipient compatibility knowledge and information are valuable in the design of formulation and manufacturing processes. Such information may be gained through theoretical investigation and experimental studies. It is known to all that mechanistic understanding of degradation kinetics provides more value in predicting stability than experimental data collected under artificial stress conditions.

Formulation Design and Development

Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive *in vitro* dissolution methods is crucial to an effective development program. FDA's recommended *in vitro* dissolution method is generally used for quality control. Generic-drug sponsors report using in-house methods for pharmaceutical development (some mentioned using as many as five biorelevant dissolution conditions) to evaluate formulations and processes before performing bioequivalence studies.

QbD should rely on the relevance of individual studies rather than the number of studies because one of the objectives of QbD is to understand how the material attributes of the drug substance and excipients influence product quality.[18]

In order to design and develop a robust generic product that has the desirable QTPP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, and aqueous solubility as function of pH, hygroscopicity, and melting points.[19-21]

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided.

Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Overages

Use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product.

Information should be provided on the-

- Amount of overage,
- Reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and
- Justification for the amount of overage.

The overage should be included in the amount of drug substance listed in the batch formula.[22]

Manufacturing Process Development

Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during

process development are the QTPP and CQAs. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process development. The selection of the type of process depends upon the formulation and the properties of the materials.

A formulation without a process is, for example, a pile of powder. Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing.

The selection of type of process depends upon the product design and the properties of the materials. For example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed. When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor. Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized.

The use of CAPD and process simulation should result in more robust processes developed faster and at a lower cost, resulting in higher quality products.[23-25]

Identification of critical process parameters (CPPS) and critical material attributes (CMAS) and critical quality attributes (CQAS) and relationship of critical quality attribute (CQAS) to critical process parameters (CPPS) and critical material attributes (CMAS) and source of variability

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. A unit operation is a discrete activity such as mixing, milling, granulation, drying, compression, or coating that involves physical or chemical changes. A physical, chemical, or microbiological property or characteristic of an input or output material is defined as a material attribute. Process parameters include the type of equipment and equipment settings, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The output of a process depends on the process parameters and the input material attributes. Process robustness is the ability of a process to demonstrate acceptable quality of the product and tolerate variability in inputs at the same time. The effects of variations in process parameters and input material attributes are evaluated in process-robustness studies. The analysis of these experiments identifies CPPs and CMAs that could affect product quality and establishes limits for these CPPs and CMAs within which the quality of drug product is assured. When the limits on CPPs and CMAs are scale-independent, they may form the basis of a design space as defined in ICH Q8 (R1). Even when a design space is not established, multivariate experiments are valuable because they identify CPPs and CMAs and support a conclusion of process robustness.

Process parameters and material attributes are critical when a practical change can result in failure for the product to meet the QTPP or a CQA that is outside an acceptable range. Process parameters are not critical when there is no trend to failure and there is no evidence of significant interactions within the proven acceptable range. It was necessary to conduct process robustness studies for each unit operation; The primary reason for this claim was that some generic-drug sponsors have sufficient prior knowledge to determine whether a process parameter or material attribute is critical or not and to know when process operating conditions will be robust. Process-robustness studies should be risk-based, that is, more studies with complex products and fewer studies with simple low-risk dosage forms.

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical,

chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training, standard operating procedure (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly. Therefore, risk assessment should be used to reduce variables to be investigated. Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. In process robustness studies, effects of variations in process parameters for a candidate process are evaluated. The analysis of these experiments identifies critical process parameters that could potentially affect product quality or performance, and establishes limits for the critical process parameters within which the quality of drug product is assured. Ideally, data used to identify process parameters should be derived from commercial scale processes to avoid any potential impact of scale-up. However, in reality, these studies are often conducted on laboratory or pilot-scale batches. If results from the small scale batches have not been shown to be size independent, any conclusion from small scale studies may need to be verified in the actual commercial production batches. At the end, the effect of raw material attributes and critical process parameters on product quality or product variability is fully understood and established. Ideally, the interactions between materials attributes and critical process parameters should be understood so that critical process parameters can be varied to compensate for changes in raw materials. To demonstrate the reproducibility and consistency of a process, process capability should be studied. Process capability is a statistical measure of the inherent process variability for a given characteristic. The most widely accepted formula for process capability is a six sigma. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:

Process capability index (CpK) = Upper limit of specification - lower limit of specification / (σ) standard deviation.

If the CpK value is significantly greater than one, the process is deemed capable. If the process capability is low, recommend an iterative five-step procedure to progressively reduce the variability of the process. These five steps are:

1. Define: The intended improvement should be clearly stated.
2. Measure: The critical product performance attributes should be measured to see if they are out of specification. The out of specification data should be analyzed and used to the sigma level of the process.
3. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.
4. Improve: The process should be redesigned and/or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.
5. Control: The improved manufacturing process should be evaluated and maintained.

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined. When considering scale-up, however, additional experimental work may be required to confirm that the model generated at the small scale is predictive at the large scale. This is because some critical process parameters are scale dependent while others do not. The operating range of scale dependent critical process parameters will have to change because of scale-up. Prior knowledge can play a very significant role in this regard as most pharmaceutical companies use the same technologies and excipients on a regular basis. Pharmaceutical scientists can often take advantage of past experience to define critical material properties, processing parameters and their operating ranges. [26-29]

IDENTIFYING CRITICAL QUALITY ATTRIBUTES (CQA)

Definition ICH Q8 (R1) defines CQAs as physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

The International Society of Pharmaceutical Engineers (ISPE) & Product Quality Lifecycle Implementation (PQLI) defines critical quality attributes (CQAs) as physical, chemical, biological or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.

CQA has been used by some to describe elements of the QTPP (such as dissolution) while others have used CQA to describe mechanistic factors (such as particle size and hardness) that determine product performance. Thus CQA is used to describe both aspects of product performance and determinants of product performance.

It was stated that the ICH working definition of CQA was: "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance". This CQA definition implies that the intended safety, efficacy, stability and performance are not CQAs. Safety and efficacy clearly fall under the domain of the TPP. But if stability and performance are not CQA and not part of the TPP, then what are they? We are thus compelled to acknowledge that there is an intermediate category of product performance (or surrogates for quality) that we have defined as the QTPP.

It seems more precise to consider the TPP, QTPP, and material attributes as separate categories. The use of CQA can be reserved for cases where there is a need to refer collectively to the targets of a QbD approach. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material.

Although many people have identified dissolution as a critical quality attribute, we consider that a set of critical material attributes (CMAs) that are independent of each other provide specific goals with which to evaluate a manufacturing process. For example a dissolution test may depend on particle size and hardness. Particle size and hardness are CMAs which can be directly linked to raw materials and manufacturing process parameters. Independent CMAs are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process. At the 2005 Drug Information Association meeting, Reed discussed dissolution in detail and indicated the greater value of has very specific CQAs. Others have commented negatively that processing behaviour of materials is usually evaluated in performance tests (flowability) rather than focusing on fundamental material properties.

Differentiating between CMAs (properties) and multi-faceted performance tests is part of the movement away from quality by testing to quality by design.

The evolution of ICH Q8 is also consistent with making a distinction between CMA and performance tests. The 2004 Q8 draft put CQA and performance tests into the same pile of physiochemical and biological properties:

The physicochemical and biological properties relevant to the performance or manufacturability of the drug product should be identified and discussed. These could include formulation attributes such as pH, osmolarity, ionic strength, lipophilicity, dissolution, redispersion, reconstitution, particle size distribution, particle shape, aggregation, polymorphism, rheological properties, and globule size of emulsions, biological activity or potency, and/or immunological activity. The TPP would be the labelling statement (supported by clinical data) that the product does not dose-dump when taken with alcohol. A performance test in the QTPP would be an in vitro dissolution test in alcohol. The critical material attributes (CMA) would be the thickness of a tablet coat. Defining the CMAs on this mechanistic physical property level makes it the best link to the manufacturing process variables.[26-27]

CRITICAL PROCESS PARAMETERS

What is a Process Parameter?

Critical process parameter (CPP) is defined as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process uniformity. In this view, every item would be a process parameter.

We propose that process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

For a given unit operation, there are four categories of parameters and attributes

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions.

What is an Unclassified Process Parameter

There are many material attributes and process parameters that are important and even essential to product quality, but it is of little value to define all parameters as critical.

Thus we propose three categories for attributes or parameters:

1. Unclassified,
2. Critical and
3. Non-critical

For example, in the granulation process, the impeller speed should clearly be identified as an unclassified

process parameter because if impeller speed were zero the process step would not be successful. However, this does not mean that impeller speed is always a critical parameter. If development studies demonstrated the granulation was not affected by realistic changes in impeller speed, it would not be identified as critical.

What is a Critical Process Parameter

A parameter is *Critical* when a realistic change in that parameter can cause the product to fail to meet the QTPP.

Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider.

A simple example is that an impeller speed of zero will always fail.

Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. The POS can also be considered as the extent of the sponsor's quality system with respect to these parameters. This definition is at the discretion of the application that sponsor must balance the trade-offs in its definition. The POS defines the scope of the application and the sponsor's quality system so that going outside of the POS must need an amendment or supplement to the application. Thus sponsors benefit from defining a large feasible POS. The cost of a large POS is the need for the pharmaceutical development (in the form of prior knowledge, process models or experimental data) to cover the POS and the increased chance that a parameter will be found critical in the large POS. The only constraint on the narrowness of the POS is that the POS must encompass the variability of the process parameters around their target values.

Our criteria for identifying critical and non-critical parameters are that a parameter is *Non-critical* when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR)(see explanatory footnote on first page of article), which is the range of experimental observations that lead to acceptable quality. A sponsor has the option of conducting experimental observations over the entire POS; in this case the POS could be equivalent to the PAR. Alternatively a sponsor may use prior knowledge, mechanistic models and trends from the PAR to draw conclusions about sensitivity over a POS that is larger than the PAR. If the lack of interaction part of the test cannot be met, then the parameter remains a UPP.

A parameter is critical when there is an observation of failure or a trend to failure predicted within the POS. If the interaction between two parameters is significant enough to predict a potential failure in the POS, then both parameters should be considered as critical. The most definitive way to identify critical and noncritical parameters is by scientific investigations involving controlled variations of the parameters.

Table 2: Classification of Process Parameters

Parameter Type	Definition	Sensitivity
Non-Critical Process parameter (Non-CPP)	Not critical	No failure in target product quality profile (TPQP) observed or predicted in the (non-CPP) potential operating space (POS),
		No interactions with other parameters in the proven acceptable range (PAR)
Unclassified Process parameter (UPP)	Criticality unknown	Not established
		The default in the absence of pharmaceutical development
Critical Process parameter (CPP)	Critical (control needed to ensure quality	Failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), or
		Interactions with other parameters in the proven acceptable range (PAR)

Uniqueness of Critical Process Parameters

Because of the broadness of the CPP definition it is possible for two investigators to examine the same process and come to a different set of CPP. The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality. Different sets of CPP can have several origins. One is that the definition of operating parameters depends on the engineering systems installed on a piece of process equipment.

Example, one fluid bed dryer may define the product temperature as an operating parameter and have an internal control system (a thermostat) that maintains that temperature, while another fluid bed dryer may have inlet air flow rate and inlet air temperature indicated as operating parameters.

Batch record for the first unit might indicate a fixed temperature, while the second unit would have a design space that indicated the combination of inlet air flow rate and inlet air temperature that would insure the appropriate product temperature.[30]

RISK ASSESSMENT AND DESIGN SPACE

Quality Risk Management (ICH Q9) indicates that, the manufacturing and use of a drug product necessarily entail some degree of risk.

Risk assessment is a valuable science based process used in science-quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs.

Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data.

Use of a risk assessment tool:

A cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies potential variables which can have an impact on the desired quality attribute

ICH Q8 (R1) defines ***Design space*** as, the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.

Many believe design space and QbD are interchangeable terms. This is incorrect. For generic-drug applications, design space is optional. QbD can be implemented without a design space because product and process understanding can be established without a formal design space. It should be pointed out that implementation of QbD is strongly encouraged by FDA. For some complex drug substances or drug products, implementation of QbD is considered a required component of the application.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations. Such relationships are arrived at by iterative application of risk assessment and experimental design, modelling, as well as the use of literature and prior experience. The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. Normal operating ranges are a subset of the Design Space and are managed under the company Pharmaceutical quality System. The Design Space may also contain operating ranges for process parameters classified in the intermediate criticality category discussed previously. Information regarding site and scale of manufacture may also be included, depending on the quality of the process knowledge upon which the Design Space is based.

In the presence of interacting critical process parameters a design space is one approach to ensure product quality although it is not a check-box requirement.

The current definition of design space is "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."

This definition evolved from early ICH Q8 drafts where design space was defined as "the established range of process parameters that has been demonstrated to provide assurance of quality". The change emphasizes the multidimensional interaction of input variables and closely binds the establishment of a design space to a conduct of a DOE that includes interactions among the input variables.

A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process.

Submission of a design space to FDA is a pathway obtaining the ability to operate within that design space without further regulatory approval. [31-35]

Scale-Up

Currently, the mechanistic understanding of pharmaceutical unit operations is limited. Scale-up is largely based on general rule-of-thumb and trial-and-error approaches. During scale-up, process parameters may vary while material attributes will not. QbD offers many more advantages for complex products than for simple ones. It was noted that scale-up can be done without QbD, but with much higher risk.

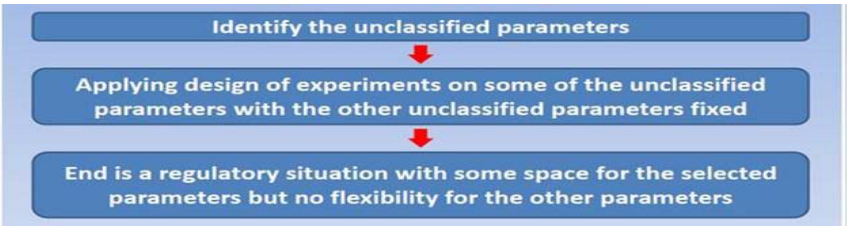

Figure 3: Steps to Design Space

DEFINING CONTROL STRATEGY

ICH Q8 (R1) defines control strategy as:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

The controls can include parameters and attributes related to:

- Drug substance,
- Drug-product materials and components,
- Facility and equipment operating conditions,
- In-process controls,
- Finished-product specifications,
- The associated methods and
- Frequency of monitoring and control. (ICH Q10)

Specifically, the control strategy may include:

- Control of input material attributes (e.g., drug substance, excipients, and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Practical controls
- Facility controls, such as utilities, environmental systems and operating conditions
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls - based on patient requirements - to be applied throughout the whole product lifecycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution.

Minimal and enhanced approaches

As in ICH Q8(R), a distinction may be drawn between a minimal and an enhanced control strategy approach.

In a *Minimal Control Strategy*, drug product quality is controlled primarily by intermediate (in process material) and end product testing.

In an *Enhanced Control Strategy* drug product quality ensured by risk-based control strategy for well understood product and process, and quality controls are shifted upstream, with the possibility of real-time release or reduced end-product testing.

Developing the control strategy

Development of a Control Strategy requires a structured process, involving a multi-disciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment.

The PQLI Control Strategy Team has proposed a Control Strategy Model that facilitates understanding and that may be used a cross-functional communication tool.

Personnel at all levels should be able to understand the way control strategy links from CQAs to operational aspects to ensure, for example that:

- Chemists understand in-process controls are established to keep the process inside the design space and seek opportunities for simplification of controls, as knowledge is gained.
- Engineers know how equipment operating conditions impact product quality.
- Quality Assurance professionals know where the highest risks are in the process.

Although the primary driver for development of a control strategy will be assurance of product safety, efficacy and quality, the Control Strategy may also ensure the meeting of other business objectives such as operator health and safety, protection of the environment, manufacturability, and supplies related issues, efficiency, and profitability. Development of a Control Strategy for a product will therefore be a structured activity involving a multi-disciplinary team of experts. This team may include representatives from formulation development, drug substance development, process development, analytical development, QC, QA, Regulatory Affairs, manufacturing, engineering, and specialists in Process Analytical Technology (PAT) and chemo-metrics.

A Control Strategy and a product release strategy are not the same, but demonstration of adherence to the Control Strategy would support the product or batch release strategy.

Control of input material attributes

Variability in the manufacturing processes may be caused by variability in the drug substance and raw materials and their attributes, when linked to a CQA. The impact of not only chemical but also physical material attributes and their variability need to be understood. For example, for an oral solid dosage product, impact of factors such as participle size distribution, particle shape distribution, density, surface area, surface energy, flow, cohesiveness, friction, elastic modulus, amorphous content, compactibility, hygroscopicity, solubility, and static charge should be assessed. A linkage between the product CQAs and the input material attributes should enable identification and understanding of the most critical material attributes and their impact on the product CQAs. Controlling the variability of input materials can be

managed in different ways, e.g. by functional specifications (not necessary in concurrence with compendia specifications) or by managing the variability directly in the process using closed loop controls. One example is raw materials affected by seasonal variations in the moisture level and used in a moisture critical blend. By applying PAT tools such as NIR (Near Infrared) spectroscopy, drying can be monitored on-line and the drying process controlled to the end-point with a closed feed-backward control loop in place. In many cases the variability in a material input can be managed by operating the process conditions differently within the Design Space. Other input materials such as packaging material should be studied during development to identify and understand which material attributes impact the manufacturing process and final product CQAs.

Real-time testing / In-process controls

Real time testing is needed to base the release the product on product and process understanding rather than on end product testing alone or on result of batch analysis.

Real time testing include all controls that need to be performed during processing, including control of Critical Process Parameters, in-process material attributes and components, as well as equipment and facility parameters that must be monitored or controlled to achieve the product CQAs.

Controlling the Critical Process Parameters during processing is important as they have a direct impact on the CQAs, but other parameters, that have an impact on downstream processing or other end-product quality attributes not already covered by a CQA, should be monitored or controlled as well. Which parameters to monitor or control is the outcome of Quality Risk Management (QRM) activities aimed at mitigating the risks arising during manufacturing.

In-process controls could include

- conventional sampling and
- At-line analysis or On-line or in-line univariate sensors or multivariate probes (typical spectroscopy)

They may be manual or automated, depending on the nature of the process itself, what needs to be measured and controlled, how often, scale, process time, and the nature of the manufacturing equipment. [36-37]

Control strategy and the product lifecycle

The Control Strategy is related to the level of process understanding at a given time, and evolves as manufacturing experience increases.

The originally specified measures, controls or models may be modified or even removed, or the need for additional controls may be identified.

Other revisions to the Control Strategy may relate to continual improvement, for example the introduction of improved analyser or control technology.

Periodic reviews of risk assessments and mitigation should be conducted to determine the appropriateness of the Control Strategy based on product manufacturing history.

Failure or deviations should be investigated and the effectiveness of the control system considered in relation to the identified root cause.

Corrective and preventive actions should be applied and the Control Strategy updated as necessary (including any regulatory actions required) in the light of new product and process knowledge.

Implementing PAT in the Control Strategy will require the application of process models (multivariate prediction models) that either predicts CQAs or CPPs or a combination of both. These models may require frequent updates, depending on the maturity of the model (e.g., the amount of data and their variability within the model), as well as the kind of data that has been included to reflect variability in scale, equipment, analytical set-up, sampling, and site.

A monitoring program for verifying the validity of process models should be established and be based on a risk analysis of the model itself and include possible ways to verify the model by other means. One example would be to compare the predicted CQA value to a conventional analytical method. The monitoring program should include requirements for when a model has to be updated (e.g. change of raw material supplier or deviations resulting in increased knowledge).

Continuous Improvement

“Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.”

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability.

The backbone for Continuous Improvement is the Pharmaceutical Quality System. PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently.

Quality risk management can be useful for identifying and prioritizing areas for continual improvement. “Continuous improvement is not the same as corrective actions preventative actions (CAPA). CAPA’s occur when product

quality characteristics are in question (e.g., out of specification). For continuous improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space"

Examples of Continuous Improvement include adjusting a set point of a process, advanced control techniques, new equipment of the same design, re-designing a process step, changing a working process, LEAN initiatives, simplifying documents, automatic a process, installing on-line measurements, removing a unit operation, changing the design space and updating the Control Strategy. [38]

"Continuous Improvement is Hallmark of QbD".

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Review Article

Understanding Pharmaceutical Quality by Design

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Abstract. This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: (1) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; (2) product design and understanding including identification of critical material attributes (CMAs); (3) process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; (4) a control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process; and (5) process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and drug application review.

KEY WORDS: control strategy; critical quality attributes; pharmaceutical quality by design; process understanding; product understanding.

INTRODUCTION

Quality by design (QbD) is a concept first developed by the quality pioneer Dr. Joseph M. Juran (1). Dr. Juran believed that quality should be designed into a product, and that most quality crises and problems relate to the way in which a product was designed in the first place. Woodcock (2) defined a high-quality drug product as a product free of contamination and reliably delivering the therapeutic benefit promised in the label to the consumer. The US Food and Drug Administration (FDA) encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing, and regulation. FDA's emphasis on QbD began with the recognition that increased testing does not necessarily improve product quality. Quality must be built into the product.

Over the years, pharmaceutical QbD has evolved with the issuance of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) (3–5). In addition, the ICH Q1WG on Q8, Q9, and Q10 Questions and Answers; the ICH Q8/Q9/Q10 Points to Consider document; and ICH Q11 (Development and Manufacture of Drug Substance) have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications (6–9). These documents provide high level directions with respect to the scope and definition of QbD as it applies to the pharmaceutical industry.

Nonetheless, many implementation details are not discussed in these guidances or documents. There is confusion among industry scientists, academicians, and regulators despite recent publications (10–13). This paper is intended to describe the objectives of pharmaceutical QbD, detail its concept and elements, and explain implementation tools and studies.

PHARMACEUTICAL QUALITY BY DESIGN OBJECTIVES

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management (3). The goals of pharmaceutical QbD may include the following:

1. To achieve meaningful product quality specifications that are based on clinical performance
2. To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
3. To increase product development and manufacturing efficiencies
4. To enhance root cause analysis and postapproval change management

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Under QbD, these goals can often be achieved by linking product quality to the desired clinical performance and then designing a robust formulation and manufacturing process to consistently deliver the desired product quality.

Since the initiation of pharmaceutical QbD, the FDA has made significant progress in achieving the first objective: performance-based quality specifications. Some examples of FDA policies include tablet scoring and bead sizes in capsules labeled for sprinkle (14,15). The recent FDA discussions on the assayed potency limits for narrow therapeutic index drugs and physical attributes of generic drug products reflect this trend (16). Nonetheless, it should be recognized that ICH documents (3–9) did not explicitly acknowledge clinical performance-based specifications as a QbD goal, although this was recognized in a recent scientific paper (10).

The second objective of pharmaceutical QbD is to increase process capability and reduce product variability that often leads to product defects, rejections, and recalls. Achieving this objective requires robustly designed product and process. In addition, an improved product and process understanding can facilitate the identification and control of factors influencing the drug product quality. After regulatory approval, effort should continue to improve the process to reduce product variability, defects, rejections, and recalls.

QbD uses a systematic approach to product design and development. As such, it enhances development capability, speed, and formulation design. Furthermore, it transfers resources from a downstream corrective mode to an upstream proactive mode. It enhances the manufacturer's ability to identify the root causes of manufacturing failures. Hence, increasing product development and manufacturing efficiencies is the third objective of pharmaceutical QbD.

The final objective of QbD is to enhance root cause analysis and postapproval change management. Without good product and process understanding, the ability to efficiently scale-up and conduct root cause analysis is limited and requires the generation of additional data sets on the proposed larger scale. FDA's change guidances (17,18) provide a framework for postapproval changes. Recently, the FDA issued a guidance intended to reduce the regulatory filing requirements for specific low-risk chemistry, manufacturing, and control (CMC) postapproval manufacturing changes (19).

ELEMENTS OF PHARMACEUTICAL QUALITY BY DESIGN

In a pharmaceutical QbD approach to product development, an applicant identifies characteristics that are critical to quality from the patient's perspective, translates them into the drug product critical quality attributes (CQAs), and establishes the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product with such CQAs to the patient. QbD consists of the following elements:

1. A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product
2. Product design and understanding including the identification of critical material attributes (CMAs)
3. Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs
4. A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process
5. Process capability and continual improvement

Quality Target Product Profile that Identifies the Critical Quality Attributes of the Drug Product

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP forms the basis of design for the development of the product. Considerations for inclusion in the QTPP could include the following (3):

- Intended use in a clinical setting, route of administration, dosage form, and delivery system(s)
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (*e.g.*, dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (*e.g.*, sterility, purity, stability, and drug release) appropriate for the intended marketed product

Identification of the CQAs of the drug product is the next step in drug product development. A CQA is a physical, chemical, biological, or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality (3). The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits, and physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical. Criticality of an attribute is primarily based upon the severity of harm to the patient should the product fall outside the acceptable range for that attribute. Probability of occurrence, detectability, or controllability does not impact criticality of an attribute.

It seems obvious that a new product should be adequately defined before any development work commences. However, over the years, the value of predefining the target characteristics of the drug product is often underestimated. Consequently, the lack of a well-defined QTPP has resulted in wasted time and valuable resources. A recent paper by Raw

et al. (12) illustrates the significance of defining the correct QTPP before conducting any development. Also, QbD examples exemplify the identification and use of QTPPs (20–22).

Product Design and Understanding

Over the years, QbD's focus has been on the process design, understanding, and control, as discussed in the ICH Q8 (R2) guidance (3). It should be emphasized that product design, understanding, and control are equally important. Product design determines whether the product is able to meet patients' needs, which is confirmed with clinical studies. Product design also determines whether the product is able to maintain its performance through its shelf life, which is confirmed with stability studies. This type of product understanding could have prevented some historical stability failures.

The key objective of product design and understanding is to develop a robust product that can deliver the desired QTPP over the product shelf life. Product design is open-ended and may allow for many design pathways. Key elements of product design and understanding include the following:

- Physical, chemical, and biological characterization of the drug substance(s)
- Identification and selection of excipient type and grade, and knowledge of intrinsic excipient variability
- Interactions of drug and excipients
- Optimization of formulation and identification of CMAs of both excipients and drug substance

To design and develop a robust drug product that has the intended CQAs, a product development scientist must give serious consideration to the physical, chemical, and biological properties of the drug substance. Physical properties include physical description (particle size distribution and particle morphology), polymorphism and form transformation, aqueous solubility as a function of pH, intrinsic dissolution rate, hygroscopicity, and melting point(s). Pharmaceutical solid polymorphism, for example, has received much attention recently since it can impact solubility, dissolution, stability, and manufacturability. Chemical properties include pKa, chemical stability in solid state and in solution, as well as photolytic and oxidative stability. Biological properties include partition coefficient, membrane permeability, and bioavailability.

Pharmaceutical excipients are components of a drug product other than the active pharmaceutical ingredient. Excipients can (1) aid in the processing of the dosage form during its manufacture; (2) protect, support, or enhance stability, bioavailability, or patient acceptability; (3) assist in product identification; or (4) enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use (23). They are classified by the functions they perform in a pharmaceutical dosage form. Among 42 functional excipient categories listed in USP/NF (24), commonly used excipients include binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colors, sweeteners, preservatives, suspending/dispersing agents, pH modifiers/buffers, tonicity agents, film formers/coatings, flavors, and printing inks. The FDA's inactive ingredients database (25) lists the safety limits of excipients based on prior use in FDA-approved drug products.

It is well recognized that excipients can be a major source of variability. Despite the fact that excipients can alter the stability, manufacturability, and bioavailability of drug products, the general principles of excipient selection are not well-defined, and excipients are often selected *ad hoc* without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 (R2) recommends drug-excipient compatibility studies to facilitate the early prediction of compatibility (3). Systematic drug-excipient compatibility studies offer several advantages as follows: minimizing unexpected stability failures which usually lead to increased development time and cost, maximizing the stability of a formulation and hence the shelf life of the drug product, and enhancing the understanding of drug-excipient interactions that can help with root cause analysis should stability problems occur.

Formulation optimization studies are essential in developing a robust formulation that is not on the edge of failure. Without optimization studies, a formulation is more likely to be high risk because it is unknown whether any changes in the formulation itself or in the raw material properties would significantly impact the quality and performance of the drug product, as shown in recent examples (26,27). Formulation optimization studies provide important information on the following:

- Robustness of the formulation including establishing functional relationships between CQAs and CMAs
- Identification of CMAs of drug substance, excipients, and in-process materials
- Development of control strategies for drug substance and excipients

In a QbD approach, it is not the number of optimization studies conducted but rather the relevance of the studies and the utility of the knowledge gained for designing a quality drug product that is paramount. As such, the QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD.

Drug substance, excipients, and in-process materials may have many CMAs. A CMA is a physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of that drug substance, excipient, or in-process material. For the purpose of this paper, CMAs are considered different from CQAs in that CQAs are for output materials including product intermediates and finished drug product while CMAs are for input materials including drug substance and excipients. The CQA of an intermediate may become a CMA of that same intermediate for a downstream manufacturing step.

Since there are many attributes of the drug substance and excipients that could potentially impact the CQAs of the intermediates and finished drug product, it is unrealistic that a formulation scientist investigate all the identified material attributes during the formulation optimization studies. Therefore, a risk assessment would be valuable in prioritizing which material attributes warrant further study. The assessment should leverage common scientific knowledge and the formulator's expertise. A material attribute is critical when a realistic change in that material attribute can have a

Table I. Typical Input Material Attributes, Process Parameters, and Quality Attributes of Pharmaceutical Unit Operations

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
	Blending/mixing	
• Particle size • Particle size distribution • Fines/oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Moisture content	• Type and geometry of mixer • Mixer load level • Order of addition • Number of revolutions (time and speed) • Agitating bar (on/off pattern) • Discharge method • Holding time • Environment temperature and RH	• Blend uniformity • Potency • Particle size • Particle size distribution • Bulk/tapped/true density • Moisture content • Flow properties • Cohesive/adhesive properties • Powder segregation • Electrostatic properties
	Size reduction/comminution	
• Particle/granule size • Particle/granule size distribution • Fines • Particle/granule shape • Bulk/tapped/true density • Adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content • Granule porosity/density	Ribbon milling • Ribbon dimensions • Ribbon density • Ribbon porosity/solid fraction Impact/cutting/screening mills • Mill type • Speed • Blade configuration, type, orientation • Screen size and type • Feeding rate Fluid energy mill • Number of grinding nozzles • Feed rate • Nozzle pressure • Classifier Granule/ribbon milling • Mill type • Speed • Blade configuration, type, orientation • Screen size and type • Feeding rate	• Particle/granule size • Particle/granule size distribution • Particle/granule shape • Particle/granule shape factor (*e.g.*, aspect ratio) • Particle/granule density/Porosity • Bulk/tapped/true density • Flow properties • API polymorphic form • API crystalline morphology • Cohesive/adhesive properties • Electrostatic properties • Hardness/Plasticity • Viscoelasticity • Brittleness • Elasticity
	Wet granulation	
• Particle size distribution • Fines/Oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content	High/low shear granulation • Type of granulator (High/low shear, top/bottom drive) • Fill level • Pregranulation mix time • Granulating liquid or solvent quantity • Impeller speed, tip speed, configuration, location, power consumption/torque • Chopper speed, configuration, location, power consumption • Spray nozzle type and location • Method of binder excipient addition (dry/wet) • Method of granulating liquid addition (spray or pump) • granulating liquid temperature • granulating liquid addition rate and time • Wet massing time (post-granulation mix time) • Bowl temperature(jacket temperature) • Product temperature • Post mixing time • Pump Type: Peristaltic, Gear type • Granulating liquid vessel (*e.g.*, pressurized, heated) Fluid bed granulation • Type of fluid bed • Inlet air distribution plate • Spray nozzle (tip size, type/quantity/ pattern/configuration/position) • Filter type and orifice size	• Endpoint measurement (*e.g.*, power consumption, torque, *etc.*) • Blend uniformity • Potency • Flow • Moisture content • Particle size and distribution • Granule size and distribution • Granule strength and uniformity • Bulk/tapped/true density • API polymorphic form • Cohesive/adhesive properties • Electrostatic properties • Granule brittleness • Granule elasticity • Solid form/polymorph

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
	• Fill level • Bottom screen size and type • Preheating temperature/time • Method of binder excipient addition (dry/wet) • Granulating liquid temperature • Granulating liquid quantity • Granulating liquid concentration/viscosity • Granulating liquid holding time • Granulating liquid delivery method • Granulating liquid spray rate • Inlet air, volume, temperature, dew point • Atomization air pressure • Product and filter pressure differentials • Product temperature • Exhaust air temperature, flow • Filter shaking interval and duration	
	Drying	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content	Fluidized bed • Inlet air volume, temperature, dew point • Product temperature • Exhaust air temperature, flow • Filter type and orifice size • Shaking interval and duration • Total drying time Tray • Type of tray dryer • Bed thickness/tray depth (depth of product per tray) • Type of drying tray liner (*e.g.*, paper, plastic, synthetic fiber, *etc.*) • Quantity carts and trays per chamber • Quantity of product per tray • Drying time and temperature • Air flow • Inlet dew point Vacuum/microwave • Jacket temperature • Condenser temperature • Impeller speed • Bleed air volume • Vacuum pressure • Microwave power • Electric field • Energy supplied • Product temperature • Bowl and lid temperature • Total drying time	• Granule size and distribution • Granule strength, uniformity • Flow • Bulk/tapped/true density • Moisture content • Residual solvents • API polymorphic form or transition • Purity profile • Moisture profile (*e.g.* product temperature *vs.* LOD) • Potency • Cohesive/adhesive properties • Electrostatic properties
	Roller compaction/chilsonation	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity	• Type of roller compactor • Auger (feed screw) type/design (horizontal, vertical or angular) • Deaeration (*e.g.*, vacuum) • Auger (feed screw) speed • Roll shape (cylindrical or interlocking). • Roll surface design (smooth, knurled, serrated, or pocketed) • Roll gap width (*e.g.*, flexible or fixed) • Roll speed • Roll pressure	• Ribbon appearance (edge attrition, splitting, lamination, color, *etc.*) • Ribbon thickness • Ribbon density (*e.g.*, envelop density) • Ribbon porosity/solid fraction • Ribbon tensile strength/breaking force • Throughput rate • API polymorphic form and transition

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
• Solid form/polymorph	• Roller temperature • Fines recycled (yes or no, # of cycles)	
	Extrusion–Spheronization	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph	• Type of extruder (screw or basket) • Screw length, pitch, and diameter • Screw channel depth • Screw blade configuration • Number of screws (single/dual) • Die or screen configuration (*e.g.*, radial or axial) • Die length/diameter ratio • Roll diameter (mm) • Screen opening diameter (mm) • Screw speed (rpm) • Feeding rate (g/min) • Type and scale of spheronizer • Spheronizer load level • Plate geometry and speed • Plate groove design (spacing and pattern) • Air flow • Residence time	• Extrudate • Density • Length/thickness/diameter • Moisture content • API polymorphic form and transition • Content uniformity • Throughput • Pellets after spheronization • Pellets size and distribution • Pellets shape factor (*e.g.* aspect ratio) • Bulk/Tapped density • Flow properties • Brittleness • Elasticity • Mechanical strength • Friability
	Hot melt extrusion	
• Particle size, distribution • Fines/oversize • Particle shape • Melting point • Density • Solid form/polymorph • Moisture content	• Screw design (twin/single) • Screw speed • Screw opening diameter (mm) • Solid and liquid feed rates • Feeder type/design • Feed rate • No. of zones • Zone temperatures • Chilling rate	• Extrudate density • Length/thickness/diameter • Polymorphic form and transition • Content uniformity • Throughput
	Tabletting	
• Particle/granule size and distribution • Fines/oversize • Particle/granule shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture	• Type of press (model, geometry, number of stations) • Hopper design, height, angle, vibration • Feeder mechanism (gravity/forced feed, shape of wheels, direction of rotation, number of bars) • Feed frame type and speed • Feeder fill depth • Tooling design (*e.g.*, dimension, score configuration, quality of the metal) • Maximum punch load • Press speed/dwell time • Precompression force • Main compression force • Punch penetration depth • Ejection force • Dwell Time	• Tablet appearance • Tablet weight • Weight uniformity • Content uniformity • Hardness/tablet breaking force/ tensile strength • Thickness/dimensions • Tablet porosity/density/solid fraction • Friability • Tablet defects • Moisture content • Disintegration • Dissolution
	Encapsulation	
• Particle/granule size and distribution • Fines/oversize • Particle/granule shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness	• Machine type • Machine fill speed • Tamping Force • No. of tamps • Auger screw design/speed • Powder bed height	• Capsule appearance • Weight • Weight uniformity • Content uniformity • Moisture content • Slug tensile strength • Disintegration • Dissolution

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
• Elasticity • Solid form/polymorph • Moisture		
	Pan coating	
• Tablet dimensions • Tablet defects • Hardness/plasticity • Density • Porosity • Moisture content	• Type of pan coater (conventional or side-vented) • Pan (fully perforated or partial perforated) • Baffle (design, number, location) • Pan load level • Pan rotation speed • Spray nozzle (type, quantity, pattern, configuration, spray pattern) • Nozzle to bed distance • Distance between nozzles • Nozzle orientation • Total preheating time • Inlet air flow rate, volume, temperature, dew point • Product temperature • Individual nozzle spray rate • Total spray rate • Atomization air pressure • Pattern air pressure • Exhaust air temperature, air flow • Total coating, curing time and drying time	• Coating efficiency • Core tablet weight before and after preheating • Moisture (gain/loss) during preheating • Environmental equivalency factor • Coated drug product (*e.g.*, tablet or capsule) appearance • % weight gain • Film thickness • Coating (polymer and /or color) uniformity • Hardness/breaking force/Tensile strength • Friability • Moisture (gain/loss) during overall process • Residual solvent(s) • Disintegration • Dissolution • Tablet defects • Visual attributes
	Fluid bed coating	
• Tablet dimensions • Tablet defects • Hardness/plasticity • Density/porosity moisture content	• Type of fluid bed coater • Fluid bed load level • Partition column diameter • Partition column height • Number of partition columns • Air distribution plate type and size • Filter type and orifice size • Filter differential pressure • Filter shaking interval and duration • Spray nozzle (type, quantity, pattern, configuration) • Nozzle port size • Total preheating time • Spray rate per nozzle • Total spray rate • Atomization air pressure • Inlet air flow rate, volume, temperature, dew point • Product temperature • Exhaust air temperature, air flow • Total coating, curing and drying time	• Coating efficiency • Core tablet weight before and after preheating • Moisture (gain/loss) during preheating • Environmental equivalency factor • Coated drug product (*e.g.*, tablet or capsule) appearance • % weight gain • Film thickness • Coating (polymer and /or color) uniformity • Hardness/breaking force/tensile strength • Friability • Moisture (gain/loss) during overall process • Residual solvent(s) • Disintegration • Dissolution • Tablet defects • Visual attributes
	Laser drilling	
• Size/dimensions • Polymer type membrane thickness	• Conveyor type • Conveyor speed • Laser power • Number of pulses • Type(s) of lens(es) • One or two sided • Number of holes	• Opening diameter (internal and external) • Depth • Shape of the opening

significant impact on the quality of the output material. Product understanding includes the ability to link input CMAs to output CQAs. The steps taken to gain product understanding may include the following:

1. Identify all possible known input material attributes that could impact the performance of the product
2. Use risk assessment and scientific knowledge to identify potentially high risk attributes
3. Establish levels or ranges of these potentially high-risk material attributes
4. Design and conduct experiments, using DoE when appropriate
5. Analyze the experimental data and, when possible, apply first principle models to determine if an attribute is critical
6. Develop a control strategy. For critical material attributes, define acceptable ranges. For noncritical material attributes, the acceptable range is the range investigated. When more than one excipient is involved, these defined acceptable ranges may be termed formulation design space

Process Design and Understanding

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. Unit operations may be executed in batch mode or in a continuous manufacturing process. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when (1) all critical sources of variability are identified and explained, (2) variability is managed by the process, and (3) product quality attributes can be accurately and reliably predicted (28).

Process parameters are referred to as the input operating parameters (*e.g.*, speed and flow rate) or process state variables (*e.g.*, temperature and pressure) of a process step or unit operation. A process parameter is critical when its variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Table I lists the typical manufacturing unit operations, material attributes, process parameters, and quality attributes for solid oral dosage forms.

Process robustness is the ability of a process to deliver acceptable drug product quality and performance while tolerating variability in the process and material inputs (29). The effects of variations in process parameters and material attributes are investigated in process robustness studies. The analysis of these experiments identifies CPPs that could affect drug product quality and establishes limits for these CPPs (and CMAs) within which the quality of drug product is assured. The relationship between input CMAs and CPPs and output CQAs is shown in Fig. 1.

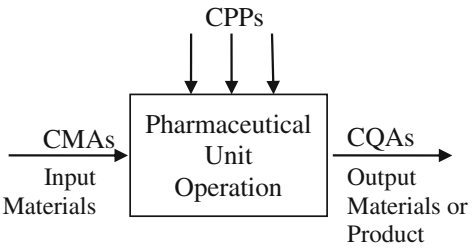
Steps to establish process understanding are very similar to those of product understanding and include the following:

1. Identify all possible known process parameters that could impact the performance of the process
2. Use risk assessment and scientific knowledge to identify potentially high-risk parameters
3. Establish levels or ranges of these potentially high-risk parameters
4. Design and conduct experiments, using DoE when appropriate
5. Analyze the experimental data and, when possible, determine scalability and apply first principle models to determine if a process parameter is critical. Link CMAs and CPPs to CQAs when possible.
6. Develop a control strategy. For critical parameters, define acceptable ranges. For noncritical parameters, the acceptable range is the range investigated. When more than one process parameter or material attribute is involved, these defined acceptable ranges may be termed process design space

While developing a strategy for investigating both product design and understanding and process design and understanding, studies can be designed in such a way that both the objectives of product and process understanding are achieved simultaneously. In addition, an interactive (or interdependent) relationship among material attributes, process parameters, and product attributes can be more easily developed when such analyses are performed in carefully planned and designed experimental studies.

ICH Q8 (R2) defines design space as the multidimensional combination and interaction of input variables (*e.g.*, material attributes) and process parameters that have been demonstrated to provide assurance of quality (3). Parameter movements that occur within the design space are not subjected to regulatory notification. However, movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus, design space is the direct outcome of analysis of the DoE data or validated models such as first-principle models.

Design space may be scale and equipment dependent. Therefore, the design space determined at laboratory scale may need to be justified for use at commercial scale. Approaches for justification may include geometric considerations, kinematic considerations, heat and mass transfer, or dimensionless numbers as well as continual verification during commercial manufacturing. Justification is needed because the mechanistic understanding of pharmaceutical unit operations may be limited and scale-up is largely based on general rule of thumb and trial-and-error approaches; however, when mechanistic understanding or reliable



$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Fig. 1. Link input critical material attributes (*CMAs*) and critical process parameters (*CPPs*) to output critical quality attributes (*CQAs*) for a unit operation

empirical models (*i.e.*, extensive process understanding) exists, then the design space can be translated across scale.

Pharmaceutical products are frequently manufactured by a combination of unit operations. For example, tablets prepared by direct compression may simply involve blending and compression. However, when tablets are prepared by wet granulation, unit operations may involve blending, granulation, wet milling, drying, dry milling, blending for lubrication, compression, coating, and packaging. In such cases, the output of the first unit operation becomes an input of subsequent unit operations. Process understanding could be conducted on each unit operation or a combination of unit operations to determine CMAs, CPPs, and CQAs. Figure 2 shows an example how the CMAs and CPPs were determined, using an example of an immediate release dosage form (20).

Control Strategy

The knowledge gained through appropriately designed development studies culminates in the establishment of a control strategy. As shown in Fig. 3, control strategy could include three levels of controls as follows:

Level 1 utilizes automatic engineering control to monitor the CQAs of the output materials in real time. This level of control is the most adaptive. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs consistently conform to the established acceptance criteria. Level 1 control can enable real-time release testing and provides an increased level of quality assurance compared to traditional end-product testing. It should be noted that adoption of process analytical technology (PAT) is not the only way to implement real-time release testing (*e.g.*, the use of predictive models as a surrogate for traditional release test, where the model may be defined in terms of traditional in-process measurements).

Level 2 consists of pharmaceutical control with reduced end-product testing and flexible material attributes and process parameters within the established design space. QbD fosters product and process understanding and facilitates identification of the sources of variability that impact product quality. Understanding the impact that variability has on in-process materials, downstream processing, and drug product quality provides an opportunity to shift controls upstream and to reduce the reliance on end-product testing (3).

Level 3 is the level of control traditionally used in the pharmaceutical industry. This control strategy relies on extensive end-product testing and tightly constrained material attributes and process parameters. Due to limited characterization of the sources of variability and inadequate understanding of the impact that CMAs and CPPs have on the drug product CQAs, any significant change in these requires regulatory oversight. Significant industry and regulatory resources are spent debating issues related to acceptable variability, the need for additional controls, and the establishment of acceptance criteria.

In reality, a hybrid approach combining levels 1 and 2 can be used. ICH Q8 (R2) (3) defines a control strategy as a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. A control strategy can include, but is not limited to, the following (3):

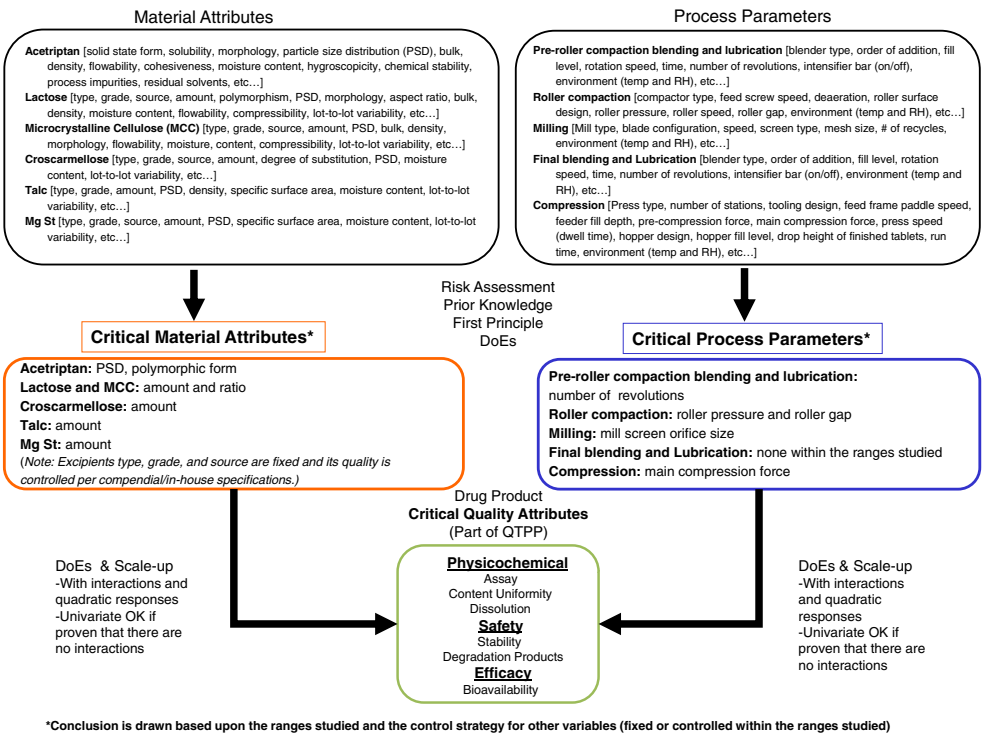


Fig. 2. Product and process understanding: an example for immediate release dosage forms

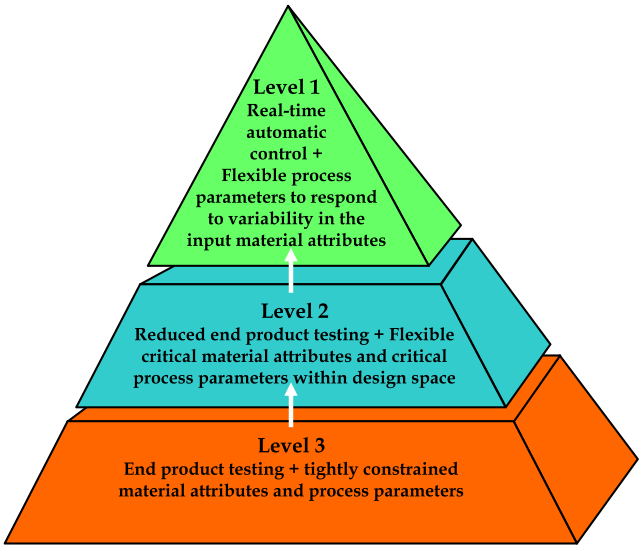


Fig. 3. Control strategy implementation options

- Control of input material attributes (*e.g.*, drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or product quality (*e.g.*, the impact of drying on degradation and particle size distribution of the granulate on dissolution)
- In-process or real-time release testing in lieu of end-product testing (*e.g.*, measurement and control of CQAs during processing)
- A monitoring program (*e.g.*, full product testing at regular intervals) for verifying multivariate prediction models

Process Capability and Continual Improvement

Process capability measures the inherent variability of a stable process that is in a state of statistical control in relation to the established acceptance criteria. Table II shows the definition, calculation formula, and description of process capability indices (30) that are useful for monitoring the performance of pharmaceutical manufacturing processes. Calculations based on the inherent variability due to common cause of a stable process (*i.e.*, in a state of statistical control) result in process capability (C_p and C_{pk}) indices. When the process has not been demonstrated to be in a state of statistical control, the calculation needs to be based on sample standard deviation of all individual (observed) samples taken over a longer period of time; the result is a process performance index (P_p and P_{pk}). A state of statistical control is achieved when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process (31).

When a process is not in a state of statistical control, it is because the process is subject to special cause (source of intermittent variation in a process). Special causes can give rise to short-term variability of the process or can cause long-term shifts or drifts of the process mean. Special causes can also create transient shifts or spikes in the process mean. On the other hand, common cause is a source of inherent variation that is random, always present, and affects every outcome of the process. In a QbD development process, the product and process understanding gained during pharmaceutical development should result in early identification and mitigation of potential sources of common cause variation *via* the control strategy. The manufacturing process will move toward a state of statistical control, and, once there, the manufacturer will continue to improve process capability by reducing or removing some of the random causes present and/or adjusting the process mean towards the preferred target value to the benefit of the patient. In a non-QbD approach, common cause variation is more likely to be discovered during commercial production and may interrupt commercial production and cause drug shortage when it will require a root cause analysis.

Process capability can be used to measure process improvement through continuous improvement efforts that focus on removing sources of inherent variability from the process operation conditions and raw material quality. Ongoing monitoring of process data for C_{pk} and other measures of statistical process control will also identify when special variations occur that need to be identified and corrective and preventive actions implemented.

Continuous improvement is a set of activities that the applicant carries out in order to enhance its ability to meet requirements. Continual improvements typically have five phases as follows (32):

- Define the problem and the project goals, specifically
- Measure key aspects of the current process and collect relevant data
- Analyze the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect if any.

Table II. Process Capability Indices and Their Measures

Index	Description
$C_p = \frac{(USL-LSL)}{6\widehat{\sigma}}$	Estimates process capability when the data mean is centered between upper and lower specification limits.
$C_{pkl} = \frac{(Mean-LSL)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of a lower limit only.
$C_{pku} = \frac{(USL-Mean)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of an upper limit only.

USL upper specification limit, *LSL* lower specification limit, $\widehat{\sigma}$ (*sigma hat*) inherent variability due to common cause of a stable process

- Improve or optimize the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

In addition, continuous improvement can apply to legacy products. Legacy products usually have a large amount of historical manufacturing data. Using multivariate analysis to examine the data could uncover major disturbances in the form of variability in raw materials and process parameters. Continuous improvement could be achieved by reducing and controlling this variability. Newer processes associated with a design space facilitate continuous process improvement since applicants will have regulatory flexibility to move within the design space (ICH Q8).

PHARMACEUTICAL QUALITY BY DESIGN TOOLS

Prior Knowledge

Although not officially defined, the term "prior knowledge" has been extensively used in workshops, seminars, and presentations. In regulatory submissions, applicants often attempt to use prior knowledge as a "legitimate" reason for substitution of scientific justifications or conducting necessary scientific studies.

Knowledge may be defined as a familiarity with someone or something, which can include information, facts, descriptions, and/or skills acquired through experience or education. The word "prior" in the term "prior knowledge" not only means "previous," but also associates with ownership and confidentiality, not available to the public. Thus, for the purpose of this paper, prior knowledge can only be obtained through experience, not education. Knowledge gained through education or public literature may be termed public knowledge. Prior knowledge in the QbD framework generally refers to knowledge that stems from previous experience that is not in publically available literature. Prior knowledge may be the proprietary information, understanding, or skill that applicants acquire through previous studies.

Risk Assessment

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk.… The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk (4)." The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development. However, the risk assessment tools identified in ICH Q9 are applicable to risk assessment in product development also.

The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product. It helps to prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which facilitates the establishment of a control strategy. The outcome of the risk assessment is to identify the variables to be experimentally investigated. ICH Q9 (4) provides a nonexhaustive list of common risk assessment tools as follows:

- Basic risk management facilitation methods (flowcharts, check sheets, *etc.*)
- Fault tree analysis
- Risk ranking and filtering
- Preliminary hazard analysis
- Hazard analysis and critical control points
- Failure mode effects analysis
- Failure mode, effects, and criticality analysis
- Hazard operability analysis
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality.

Mechanistic Model, Design of Experiments, and Data Analysis

Product and process understanding is a key element of QbD. To best achieve these objectives, in addition to mechanistic models, DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a prespecified design. The DoE also reveals relationships between input factors and output responses. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed. The strength of DoE over the traditional univariate approach to development studies is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be integrated with mechanism-based studies to maximize product and process understanding.

When DoE is applied to formulation or process development, input variables include the material attributes (*e.g.*, particle size) of raw material or excipients and process parameters (*e.g.*, press speed or spray rate), while outputs are the critical quality attributes of the in-process materials or final drug product (*e.g.*, blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release). DoE can help identify optimal conditions, CMAs, CPPs, and, ultimately, the design space. FDA scientists have shown the use of DoE in product and process design in recent publications (33–39).

Process Analytical Technology

The application of PAT may be part of the control strategy (28). ICH Q8 (R2) identifies the use of PAT to

ensure that the process remains within an established design space (3). PAT can provide continuous monitoring of CPPs, CMAs, or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space. In-process testing, CMAs, or CQAs can also be measured online or inline with PAT. Both of these applications of PAT are more effective at detecting failures than end-product testing alone. In a more robust process, PAT can enable active control of CMAs and/or CPPs, and timely adjustment of the operating parameters if a variation in the environment or input materials that would adversely impact the drug product quality is detected.

Application of PAT involves four key components as follows (40):

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management

Multivariate data acquisition and analysis requires building scientific understanding about a process and identifying critical material attributes and process parameters that affect product quality and integrating this knowledge into the process control, which is essentially the same as the process understanding in the context of QbD. Process analytical chemistry tools provide real-time and *in situ* data about the status of the process. Multivariate data analysis takes the raw information from the PAT tools and connects it to CQAs. Based on the outcome of the data analysis, process controls adjust critical variables to assure that CQAs are met. The information collected about the process provides a basis for further process optimization. Studies in FDA laboratories indicated the promise of several PAT tools and chemometric approaches (41–44).

CONCLUSION

The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and postapproval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, product design and understanding, process design and understanding, and scale up, control strategy, and continual improvement. Prior knowledge, risk assessment, DoE, and PAT are tools to facilitate QbD implementation. Finally, product and process capability is assessed and continually improved postapproval during product lifecycle management.

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STUDY MATERIAS OF ADD-ON COURSE OFFERED BY THE INSTITUTION

Name of add on course: Sigma Plot: A Tool for Statistical Analysis

Link

1. **https://www.alfasoft.com/docs/sigmaplot-tutorial.pdf**
2. **https://www.youtube.com/watch?v=oL5FsiCuEMc**
3. **https://www.youtube.com/watch?v=YZZ4_N2dnLQ**
4. **https://www.youtube.com/watch?v=WLeSu3kPEUw&t=25s**
5. **https://www.youtube.com/watchv=WLeSu3kPEUw&t=37s**

Name of add on course: Pharmacokinetic Modelling Programme

Link: https://www.aplanalytics.com/pharmacokinetics.php

1 What is yoga and the importance of yoga?

The word yoga orginates from the sanskrit word "yuj" means "to join" or "to yoke together" "to unify" "to unite as one.

Importance of yoga?

Our mental and physical health. yoga helps in keeping helps to connect to nature. Our body becomes more flexible and develops a great sense of self descipline and self awarness improves our well-being and gives us better mental clarity. The ultimate aim of yoga is self-realization. primary goal of yoga is to gain balance and control in ones life. Yoga provide a sense of calm that comes from the practice of yogic ~~asanas~~ asanas and pranayama. The practice of yogic asanas aims at overcoming the limitations of the body. When our physical state is not perfect it causes an imbalance in our mental state. The practice of yoga helps us to overcome such imbalance. ~~When~~ When there is perfect harmoney beteen the mind and body we achive total balance and control.

yoga helps us to overcome the obstacles in our life. Regular practice of stretches, twists bends, and inversion restores strength and stamina in the body. practicing yoga asanas cleanses and detoxifies the body by increasing the circulation of fresh blood through the body. Yoga poses tone the whole body, they strengthen bones and muscles, correct the posture, improve breathing and increase energy. Yoga increases the intake of oxygen and enhances the functions of all body systems, including respiratory, digestive endocrine, reproductive, and excretory systems.

2 What is pranayama?

The word prana means "life force" energy" while ayama means "control by stretching / expandency.

Hence pranayama translates to control of the life force.

3 What is Kumbhaka?

Kumbhaka means air is retained internaly or externaly

4 Who is the father of yoga?

patanjaly

8 steps of asthanga yoga

① yama, ② Niyama ③ Asanas, ④ Pranayama
⑤ pratyahara, ⑥ Dharana, ⑦ Dhyana,
⑧ Samadhi.

5 What is shat kriya and the name

of the internal organs can be cleansed by yogic techniques called Shat kriya.

Shat is a Sanskrit word - meaning six and kriya means action.

Kriyas help to remove waste materials from our internal organs.

① Dhauti ② Basti, ③ Neti, ④ Trataka

⑤ Nauli, ⑥ Kapalabhati

6 What is mudra?

Mudra is sanskrit term means gesture or attitude.

Mudras help to link the brain to the body - soothe pain, ~~Stimu~~ stimulate ~~end~~. endorphins, change the mood and increase our vitality.