Unit-2

Industrial Pharmacy 2

B.Pharma 7 Sem Notes

Unit: 2

Technology development and transfer:

- **WHO guidelines for Technology Transfer(TT):** Terminology, Technology transfer protocol, Quality risk management, Transfer from R & D to production (Process, packaging and cleaning), Granularity of TT Process (API, excipients, finished products, packaging materials) Documentation, Premises and equipments, qualification and validation, quality control, analytical method transfer, Approved regulatory bodies and agencies, Commercialization – practical aspects and problems (case studies), TT agencies in India – APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI; TT related documentation – confidentiality agreement, licensing, MoUs, legal issues

Introduction to Technology Transfer

Technology Transfer (TT) is a critical process in the pharmaceutical industry that involves the systematic movement of knowledge, data, skills, and documented procedures from one site or organization (sending unit) to another (receiving unit). The primary objective is to enable the receiving unit to produce a product or perform a service consistently, meeting predefined quality standards.

WHO defines technology transfer as: "a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and/or commercialization to an appropriate, responsible, and authorized party."

WHO Guidelines for Technology Transfer — Terminology

Definitions:

Term	Definition
Technology Transfer (TT)	Movement of technology from one place to another such that the receiving unit can perform the technology independently
Sending Unit (SU)	The organization or department that transfers the knowledge, process, or documentation
Receiving Unit (RU)	The organization or department that receives and implements the technology
Technology Package	All documentation, data, and information required for successful TT (including formulas, SOPs, validations)
Transfer Protocol	A document specifying the objectives, strategies, responsibilities, and criteria for TT
Gap Analysis	Assessment of the differences between the capabilities of the SU and RU
Technology Readiness Level	Measurement system to assess the maturity of technology for TT
Process Understanding	Understanding of the relationship between process inputs and outputs (ICH Q8)
Comparability Protocol	Pre-defined plan for evaluating comparability of products before and after changes
Scale-up	Process of transferring technology from lab/pilot scale to production scale

Regulatory Basis

- WHO Technical Report Series 961, Annex 7 (2011): Primary WHO guideline for TT in pharmaceutical manufacturing

- ICH Q8 (R2): Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ICH Q11: Development and Manufacture of Drug Substances
- 21 CFR Part 211: US FDA cGMP regulations
- EU GMP Annex 15: Qualification and Validation

Technology Transfer Protocol

Components of a TT Protocol

A formal TT Protocol is a master document that defines the scope, responsibilities, and evaluation criteria for the transfer. It must be approved before transfer activities begin.

Element	Description	Responsibility
Scope & Objectives	Define what is being transferred — process, product, method	SU + RU
Technology Description	Summary of product/process history, key attributes	SU
Acceptance Criteria	Pre-defined limits for each critical parameter	SU + RU + QA
Transfer Plan & Timeline	Milestones, activities, and deadlines	Project Manager
Risk Assessment	QRM analysis; identification of critical transfer risks	SU + RU
Training Plan	Training requirements for RU personnel	SU
Documentation List	All documents to be transferred (SOPs, specifications, BPRs)	SU + QA
Analytical Support	Methods and tools transferred for QC testing	SU QC Lab
Deviation Management	Process for managing and documenting deviations	QA
Approval Signatures	Authorization from both SU and RU	Management/QA

Stages of TT Protocol Execution

1. Pre-transfer phase: Gap analysis, feasibility study, documentation review
2. Transfer phase: Training, trial runs, knowledge transfer sessions
3. Evaluation phase: Comparison of process/product data at SU vs RU
4. Completion phase: Validation batches, regulatory filing, close-out report

Quality Risk Management (QRM) in Technology Transfer

ICH Q9 Framework Applied to TT

Quality Risk Management is a systematic process for the assessment, control, communication, and review of risks to the quality of medicinal products. In TT, QRM ensures that all critical risks are identified and mitigated before and during the transfer.

QRM Step	Activities in TT	Tools Used
Risk Identification	Identify all risks associated with the process, product, and equipment differences	Brainstorming, HAZOP, FMEA
Risk Analysis	Determine probability of occurrence and severity of harm	Risk ranking matrix, Fault Tree Analysis
Risk Evaluation	Compare identified risk to acceptance criteria	Risk scoring, risk matrix
Risk Control	Risk reduction and acceptance measures (SOPs, training, IPC)	CAPA, change control
Risk Communication	Document and communicate risks to all stakeholders	Risk register, TT protocol
Risk Review	Re-evaluate risks post-transfer using data from validation batches	Periodic review meetings

Critical Quality Attributes (CQA) in QRM

- Identify CQAs early in the TT process
- Establish design space based on CQAs and CPPs (Critical Process Parameters)
- Use Process Analytical Technology (PAT) for real-time monitoring
- Apply FMEA to rank failure modes by Risk Priority Number (RPN = Severity x Occurrence x Detectability)

Transfer from R&D to Production

Process Transfer

Process transfer involves transferring all knowledge related to the manufacturing process from the development team to the production team. This is the most critical and complex aspect of TT.

Phase	Key Activities	Critical Considerations
Pre-Formulation	Transfer of physicochemical data, solid-state characterization	Polymorphism, stability, solubility
Formulation Development	Transfer of formulation rationale, component ratios, manufacturing steps	Compatibility, excipient grades, critical steps
Process Development	Transfer of process parameters, equipment selection, in-process controls	Scale-up factors, equipment equivalence
Analytical Method	Transfer of test methods, reference standards, system suitability	Method validation, specificity, linearity
Pilot Scale	Conduct engineering batches at pilot scale at RU	3 pilot batches recommended by WHO
Validation	Process validation at commercial scale	PPQ batches (minimum 3 consecutive)

Packaging Transfer

- Primary packaging specifications: material, dimensions, closure integrity
- Packaging process parameters: sealing temperature, torque, line speed
- Container-Closure System (CCS) compatibility studies
- Stability studies with transferred packaging configuration
- Serialization and track-and-trace requirements per regulatory jurisdiction
- Artwork and labelling transfer: IPC for legibility, content, translations

Cleaning Transfer

- Transfer of validated cleaning procedures from SU to RU
- Acceptance criteria for cleaning validation: MACO (Maximum Allowable Carryover), visual inspection limits, swab/rinse sampling
- Equipment train and worst-case product identification
- Cleaning agent compatibility and rinsing verification
- TOC (Total Organic Carbon) and conductivity testing as monitoring tools

Granularity of the Technology Transfer Process

Granularity refers to the level of detail and specificity required in technology transfer for each component. WHO and ICH guidelines specify different levels of granularity for different materials and products.

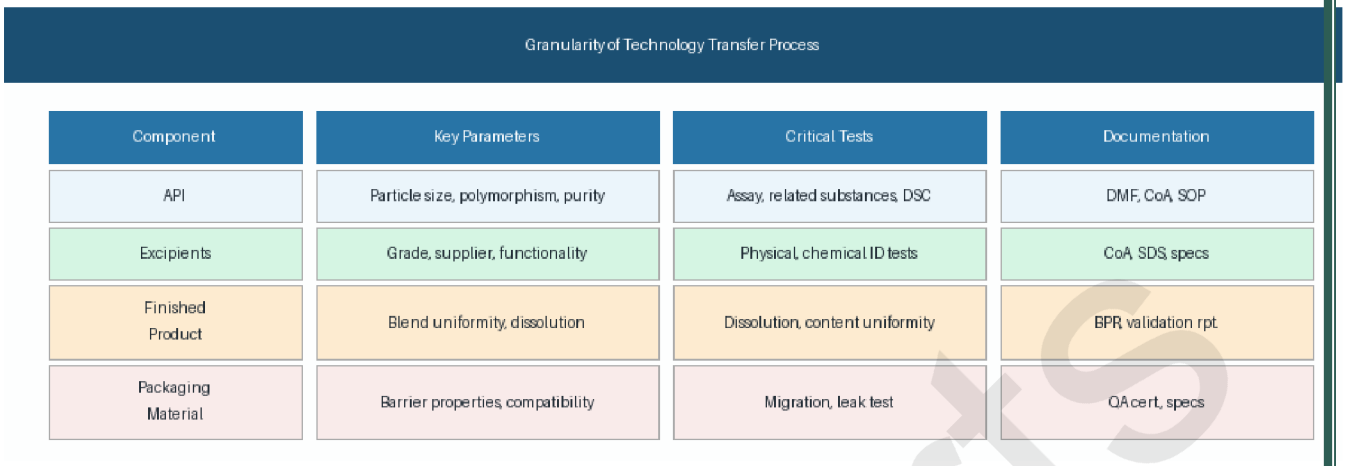

Fig 2: Granularity of TT Process — Key Parameters by Component Type

API (Active Pharmaceutical Ingredient)

Parameter	Detail Required
Chemical & Physical Properties	Purity, particle size distribution, polymorphic form, solubility, pKa, log P
Manufacturing Route	Synthetic route, reagents, solvents, reaction conditions, impurity profile
Analytical Methods	HPLC, GC, NMR, IR, dissolution, particle size analysis
Stability Profile	Stability under ICH conditions; photostability, stress testing results
Critical Quality Attributes	Identity, assay, related substances, residual solvents, heavy metals, microbial limits

Excipients

- Functional role in formulation (binder, disintegrant, lubricant, etc.)
- Grade specifications (e.g., Pharmacopoeia grade: USP, BP, Ph. Eur.)
- Supplier qualification and vendor change protocols
- Physical and chemical tests: identification, loss on drying, particle size
- Compatibility with API and other excipients

Finished Products

- Formulation composition and manufacturing instructions (Master Formula)
- In-process controls (IPCs): blend uniformity, granule moisture, tablet hardness, compression force
- Finished product specifications: dissolution, content uniformity, appearance, friability
- Stability program: ICH zones (I-IVb); real-time and accelerated stability

- Pack configuration and shelf life

Packaging Materials

- Primary packaging: blister foil (PVDC, ALU-ALU), glass vials, HDPE bottles — specifications and tests
- Secondary packaging: cartons, inserts — artwork specifications
- Functional tests: seal strength, WVTR (water vapour transmission rate), oxygen transmission
- Supplier qualification and change control

Documentation in Technology Transfer

Core Documents to be Transferred

Document Type	Content	Custodian
Technology Transfer Plan	Overview, scope, timelines, responsibilities	TT Manager
Technology Package	All technical files: formulation, process, analytical methods	SU
Master Formula Record (MFR)	Quantitative formula, manufacturing instructions, specifications	R&D / Manufacturing
Batch Manufacturing Record (BMR)	Step-by-step instructions for each batch	Manufacturing QA
Standard Operating Procedures (SOPs)	Procedures for all processes, equipment, testing	Department Heads
Analytical Test Methods	Validated methods for all specifications	QC Lab
Validation Master Plan (VMP)	Overview of all validation activities planned at RU	Validation Team
Specifications (API, FP, PM)	Release and shelf-life specifications	QC / QA
Stability Protocols & Reports	ICH stability study protocols and data	R&D / QA
Risk Assessment Reports	QRM outcomes, FMEA, control strategies	QA
Transfer Completion Report	Summary of all transfer activities and outcomes	TT Manager + QA

Premises and Equipment

Premises Requirements

- Environmental conditions: temperature, humidity, pressure differentials must match SU requirements
- Cleanroom classification (ISO 8 for oral solids, ISO 7/6 for sterile products)
- Dedicated areas for weighing, granulation, compression, coating, packaging
- Containment facilities for highly potent APIs (HPAPIs): OEB 3–5 compliance
- Water systems: WFI, purified water — must meet Ph. Eur./USP specifications
- HVAC design: unidirectional airflow in critical zones, HEPA filtration

Equipment Qualification

Qualification Stage	Purpose
Design Qualification	Verify that equipment design meets requirements before purchase
Installation Qualification	Confirm equipment is installed correctly per manufacturer specifications
Operational Qualification	Verify equipment operates within specified limits across its operating range
Performance Qualification	Demonstrate that equipment consistently performs as intended in actual use
Continued Process Verification	Ongoing monitoring during routine production to ensure maintained state of control

- Equipment equivalence assessment: when RU equipment differs from SU, a formal equivalence study must be performed
- Critical process equipment: fluid bed dryer, granulator, tablet press, coating machine, autoclave, lyophilizer
- Equipment calibration and preventive maintenance (PM) schedules must be in place

Qualification and Validation

Process Validation Stages (FDA Process Validation 2011)

Stage	Activities
Stage 1 — Process Design	Capture knowledge from development and scale-up; define CQAs, CPPs, and design space; establish control strategy
Stage 2 — Process Qualification (PPQ)	Confirm process design reproducibility using commercial-scale batches (minimum 3 PPQ batches recommended)
Stage 3 — Continued Process Verification	Ongoing assurance of process control; statistical monitoring of trends; Annual Product Review (APR)

Validation Master Plan (VMP)

- Scope and purpose of the VMP
- Validation policy and responsibilities
- List of items to be validated: processes, equipment, utilities, computerized systems, analytical methods
- Acceptance criteria definitions
- Reference SOPs and guidelines
- Change control and deviation management procedures

Cleaning Validation

- Worst-case product selection based on solubility and toxicity (MACO calculation)
- Acceptance limits: 10 ppm rule, 0.1% of therapeutic dose, visually clean
- Hematotoxic substances: use PDE (Permitted Daily Exposure) limits per EMA guidance
- Validated analytical methods for surface sampling (TOC, HPLC)

Quality Control in Technology Transfer

QC Activities During TT

- Transfer of all analytical test methods from SU to RU QC laboratory
- Performance of reference standard qualification and secondary standard preparation
- Method verification and validation studies at RU
- Parallel testing during transfer: RU and SU test the same samples and compare results
- Stability programs: continuation or initiation of stability studies at RU
- Environmental monitoring: microbial monitoring of cleanrooms and equipment surfaces

In-Process Controls (IPCs)

Product Type	Critical IPCs
Oral Tablets	Blend uniformity, moisture content, granule particle size, tablet weight, hardness, friability, disintegration
Oral Capsules	Fill weight, dissolution, blend uniformity, moisture
Sterile Injectables	Bioburden, endotoxin, filter integrity, fill volume, particulate matter, container closure integrity
Topicals/Semi-solids	pH, viscosity, homogeneity, particle size, microbial limits
Biologics	pH, osmolality, turbidity, bioassay, HCP, residual host cell DNA

Analytical Method Transfer (AMT)

Types of Analytical Method Transfer

- Full transfer: Method is transferred completely; RU performs full validation
- Partial transfer: Only selected tests are transferred; abbreviated validation
- Comparative testing: RU and SU test same samples; no independent validation required if statistical equivalence is demonstrated
- Waiver: No testing required if RU laboratory already uses identical method

AMT Protocol Requirements

Element	Detail
Method Description	Fully detailed SOP for the analytical method
Scope of Transfer	Which tests, sample types, matrices are included
Pre-transfer activities	Training, reference standard preparation, system suitability qualification
Acceptance Criteria	Statistical criteria: mean, relative bias, precision (RSD%), equivalence limits
Analytical Performance Characteristics	Specificity, linearity, range, accuracy, precision, LOD, LOQ, robustness
Sample Set	Minimum sample set (typically 3 lots, multiple concentrations) per USP/Ph. Eur.
Reporting	Transfer completion report with data, deviations, and conclusions

Statistical Evaluation

- Equivalence testing using two one-sided t-tests (TOST) or confidence interval approach
- Acceptance criterion: 98% confidence interval falls within ±2% or ±5% (depending on method)
- Inter-laboratory reproducibility: compare results from SU and RU using F-test and t-test

Approved Regulatory Bodies and Agencies

Regulatory Agency	Country/Region	Relevance to TT
WHO (World Health Organization)	Global	Publishes TT guidelines (TRS 961, Annex 7); Prequalification Programme
US FDA (Food & Drug Administration)	USA	Requires prior approval supplements or changes being effected (CBE) for TT of approved products

EMA (European Medicines Agency)	European Union	Variation guidelines (Type IA, IB, II) for site changes; GMP requirements under EU Directive
CDSCO (Central Drugs Standard Control Organisation)	India	Regulates TT for drug manufacturing; requires Schedule M compliance
PMDA (Pharmaceuticals & Medical Devices Agency)	Japan	ICH CTD submissions; site change variation procedures
Health Canada	Canada	Supplemental NDS/ANDS for manufacturing site changes
TGA (Therapeutic Goods Administration)	Australia	S4 changes for manufacturing site TT
MHRA (Medicines & Healthcare Products Regulatory Agency)	UK	Post-Brexit; Variations (Type I/II) for site changes
ANVISA	Brazil	GGMED/RE-1003 for technology transfer authorization in Brazil
NMPA (National Medical Products Administration)	China	Requires TT registration supplement for imported products

Commercialization — Practical Aspects and Case Studies

Practical Aspects of TT for Commercialization

Aspect	Considerations
Product Selection	Market potential, patent expiry, regulatory pathway, therapeutic gap, strategic fit
Site Selection	Regulatory approval status, capacity, technical capability, proximity, cost
Technology Package Completeness	All dossier data must be complete; gaps lead to regulatory delays
Regulatory Strategy	Determine filing strategy early: WHO PQ, FDA ANDA/NDA, CDSCO, etc.
Intellectual Property	Freedom to operate analysis; licensing agreements if patents are active
Commercial Scale-Up	Engineering runs, PPQ batches before commercial production
Supply Chain	Qualify API and excipient suppliers at RU; establish QA agreements
Post-Transfer Monitoring	Annual Product Review (APR); process capability monitoring; change control

Common Problems in Commercialization

- Scale-up failures: Unresolved mixing, granulation, or coating issues at larger scale
- Equipment differences: Non-equivalent equipment causing product attribute deviations
- Regulatory non-compliance: Missing data, inadequate validation, or incomplete dossiers
- Intellectual Property (IP) disputes: Undisclosed patent encumbrances
- Knowledge gaps: Tacit knowledge not captured; dependence on key personnel at SU
- Timeline delays: Underestimated complexity of TT; supply chain disruptions
- Quality deviations: Drift in product quality post-transfer due to process variability

Case Studies

Case Study 1: TT of Generic Metformin HCl 500 mg tablets — R&D to Greenfield Plant

A generic manufacturer transferring metformin tablet production to a new facility encountered scale-up problems in the wet granulation step. The planetary mixer at the SU was replaced by a high-shear granulator at the RU. Without a proper equipment equivalence study, the granule particle size distribution shifted, causing dissolution failures. Resolution: A formal equipment equivalence study with impeller tip speed calculation and granule characterization was performed. Process parameters were reoptimized at the new scale, and 3 PPQ batches confirmed successful TT.

Case Study 2: API TT for Antiretroviral Drug — PEPFAR Programme

A WHO-PQ-approved Indian manufacturer transferred its lopinavir/ritonavir API manufacturing process to a new site to scale up production under PEPFAR. Key challenges included polymorphic form control and residual solvent management. The TT involved full revalidation of crystallization conditions, updated analytical methods for form characterization (PXRD), and cleaning validation for shared equipment. The project was completed in 18 months with successful WHO-PQ reassessment.

Case Study 3: Biologics TT — MAb Upstream and Downstream

Transfer of a monoclonal antibody process from a research institute to a contract manufacturer (CMO) involved cell banking, media preparation, upstream bioreactor operation, and downstream purification (Protein A chromatography, viral clearance). Challenges included cell culture performance variability and HCP (host cell protein) levels exceeding specifications at the CMO. Root cause: differences in dissolved oxygen control strategy. Resolution: Harmonization of DO set-points and sparger design; performance qualification confirmed acceptable product quality.

Technology Transfer Agencies in India

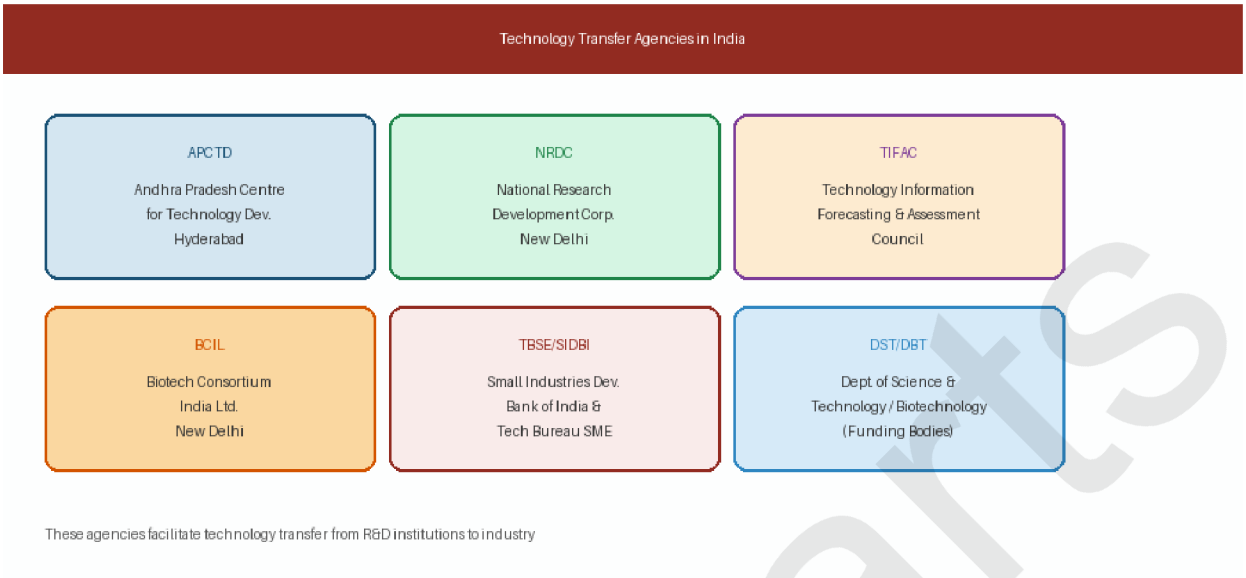

Fig 3: Major Technology Transfer Agencies in India

Agency	Full Name	Functions	Key Focus
APCTD	Andhra Pradesh Centre for Technology Development	Facilitate TT to SMEs; provide technical support; promote industry-academia linkages	AP region; food, pharma, chemical
NRDC	National Research Development Corporation	Transfer of CSIR/ICAR/ICMR technologies to industry; licensing of patents; incubation support	National; agriculture, pharma, engineering
TIFAC	Technology Information Forecasting and Assessment Council	Technology foresight; matching technology demand with available technologies; TIDP scheme	Strategic technology areas; industrial clusters
BCIL	Biotechnology Consortium India Limited	Promote biotech-industry linkage; technology commercialization; business development	Biotechnology; medical devices; diagnostics
TBSE / SIDBI	Technology Bureau for Small Enterprises / Small Industries Development Bank of India	Facilitate technology acquisition by SMEs; provide financial assistance and TT matching	SME sector; manufacturing; food processing
DBT / DST	Dept. of Biotechnology / Dept. of Science & Technology	Funding agencies; BIRAC for biotech TT; TDB (Technology Development Board) grants	Cross-sectoral; high-tech TT including biologics

NRDC — Detailed Overview

- Established in 1953 under Ministry of Science & Technology
- Has facilitated over 3,000+ technology transfers to Indian industries
- Services: Patent licensing, technology commercialization, know-how licensing, equity participation
- Sectors: Agriculture, food technology, chemicals, pharmaceuticals, electronics, mechanical engineering
- NRDC charges royalty-based licensing fees; provides technical assistance to licensees

TIFAC — Technology Foresight and Matching

- Established in 1988 under DST; autonomous body
- TIDP (Technology Innovation Development Programme): funds prototype development
- TKDL (Traditional Knowledge Digital Library): partner for traditional medicine TT protection
- Prepares Technology Vision documents for national planning

BCIL — Biotech TT in India

- Promoted by DBT (Department of Biotechnology)
- Acts as an interface between biotech R&D labs and industry
- Services: IP audit, commercialization strategy, market assessment, investor linkage
- BIRAC (Biotechnology Industry Research Assistance Council) works closely with BCIL for startup TT

Technology Transfer — Related Legal Documentation

Confidentiality Agreement (CDA/NDA)

A Confidentiality Agreement (CDA), also known as a Non-Disclosure Agreement (NDA), is the first legal document executed before sharing any proprietary information between parties.

Element	Description
Parties	Disclosing Party (DP) and Receiving Party (RP)
Definition of Confidential Information	All technical, commercial, scientific data shared during TT evaluation
Obligations of RP	Use only for evaluation; not disclose to third parties; maintain secrecy
Exclusions	Publicly available information; independently developed information; information from a third party without restriction
Duration	Typically 2–5 years; may be perpetual for trade secrets
Return/Destruction	All confidential material must be returned or destroyed upon request
Governing Law	Jurisdiction; Indian courts apply Indian Contract Act, 1872
Remedies	Specific performance and injunctive relief available for breach

Licensing Agreement

A licensing agreement grants the licensee the right to use the licensor's IP (patents, know-how, trade secrets) in exchange for consideration (royalties, lump sum, milestones).

- Exclusive License: Only one licensee; licensor cannot license to others in the same territory
- Non-exclusive License: Multiple licensees allowed
- Sub-licensing Rights: Whether licensee can further sub-license the technology
- Field of Use Restrictions: License limited to specific applications or geographies
- Royalty Structure: Running royalties (% of net sales), milestone payments, upfront fees
- Technical Assistance Clause: SU provides assistance to licensee to implement the technology
- Quality Assurance Clause: Licensee must maintain product quality standards
- Audit Rights: Licensor can audit licensee's books for royalty verification
- Termination Clauses: Conditions under which the license may be revoked

Memorandum of Understanding (MoU)

- Non-binding document that outlines the intent and framework of TT collaboration
- Covers: objectives, roles and responsibilities, timelines, financial arrangements, IP ownership
- Typically precedes a formal TT agreement; can be used as a roadmap for negotiations
- Indian government TT agreements between public institutions often use MoUs under Ministry of Science & Technology guidelines

Technology Transfer Agreement (TTA)

Clause	Key Points
Object of Transfer	Specific technology, know-how, patents, data being transferred
Payment Terms	Lump sum, milestone payments, running royalties, equity
IP Ownership	Who owns background IP, foreground IP (arising from TT), and improvements
Improvements	Whether licensee can patent improvements; back-licensing rights
Representations & Warranties	Licensor warrants that it owns the technology and has right to transfer
Indemnification	Allocation of liability for IP infringement, product defects
Confidentiality	Extended confidentiality obligations beyond NDA
Regulatory Compliance	Obligations to comply with local regulations at RU site
Force Majeure	Provisions for unforeseeable events (pandemics, natural disasters)
Dispute Resolution	Arbitration, mediation, or litigation; applicable governing law
Termination & Reversion	Conditions for termination; fate of licensed IP and technology upon termination

Legal Issues in Technology Transfer

- **Patent Issues:** Freedom-to-operate analysis; risk of infringement; Section 3(d) of Indian Patents Act — patentability of pharmaceutical TT
- **Trade Secret Protection:** Indian Trade Secrets are governed under contract law (Indian Contract Act) and tort law; no standalone TS statute
- **Compulsory Licensing:** Under TRIPS Article 31 and Section 84 of Indian Patent Act 1970; used for public health emergencies — Bayer vs Natco (2012)
- **Competition Law:** TT agreements must comply with Competition Act 2002; abuse of IP through restrictive licensing may be penalized
- **Transfer Pricing:** International TT between related parties (MNCs) subject to Income Tax Act transfer pricing rules (Sections 92-92F)
- **FEMA Compliance:** Foreign exchange aspects of international TT agreements governed by FEMA 1999

- **Export Controls:** Dual-use technology TT may require export license under SCOMET (Special Chemicals, Organisms, Materials, Equipment and Technologies) list

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