

PART III

Chemistry

Chapters 5–7 • Installment II

Molecular Chemistry

The molecule examined as a chemical object: its parts, its mirror images, its solid forms, its behavior in solution, and the spectroscopic fingerprints by which laboratories know it.

Chapter 2 introduced methamphetamine in outline. This chapter treats it as a chemist would — as a structure with definite functional groups, stereochemistry, crystalline forms, solubility behavior, stability, and spectroscopic signatures. None of this concerns how the compound is produced; it concerns what the finished compound *is*, which is precisely the knowledge that detection, identification, and quality assessment depend upon (Chapters 6 and 7).

Functional groups

Three structural features define the molecule's chemistry. The first is the **aromatic ring** — a monosubstituted benzene that gives the molecule a lipophilic, chemically robust core and a characteristic set of spectroscopic absorptions. The second is the **secondary amine**: the nitrogen bears one methyl group and one hydrogen, making it a weak organic base. With a conjugate-acid pK_a in the region of roughly 9–10, the amine is predominantly protonated (positively charged) at physiological and most environmental pH values, and it is this basicity that allows the formation of the hydrochloride salt that is the drug's usual solid form. The third is the **alkyl side chain** bearing an alpha-methyl group; that alpha-methyl substituent sterically hinders metabolism by monoamine oxidase, prolonging the molecule's action relative to the body's own phenethylamines. Together these groups explain a great deal: the aromatic ring and the alkyl chain make the free base lipophilic and membrane-permeant, while the ionizable amine makes the molecule's solubility and partitioning sharply pH-dependent.

Isomers

"Isomerism" enters the methamphetamine story in three distinct ways, and conflating them is a common error.

Enantiomers. As established in Chapter 2, the side-chain carbon bearing the methyl group is a single stereocenter, so the molecule exists as two mirror-image forms. The (S)-(+), or dextrorotary form (d-methamphetamine) is the potent central stimulant; the (R)-(-), or levorotary form (l-methamphetamine) is a weak central stimulant with predominantly peripheral (decongestant) activity. The two enantiomers are chemically identical in every scalar property — melting point, solubility, mass spectrum — and differ only in their interaction with other chiral entities, including biological receptors and chiral analytical media. This is why distinguishing them requires *chiral* methods, a point that becomes decisive in drug-test interpretation (Chapter 6).

Structural (constitutional) isomers. Methamphetamine shares its molecular formula, $C_{10}H_{15}N$, and therefore its nominal mass, with other compounds whose atoms are connected differently — phentermine being the best-known pharmaceutical example. Because such isomers have the same molecular mass, they cannot be distinguished by mass alone; they are separated by chromatography and distinguished by their full fragmentation patterns or retention behavior. This is one reason confirmatory analysis pairs a separation step with mass spectrometry rather than relying on mass measurement in isolation.

Related relatives. Methamphetamine is closely related to ephedrine and pseudoephedrine — themselves stereoisomers of one another that carry an additional hydroxyl group — and to amphetamine, its *N*-desmethyl relative and principal metabolite. These structural relationships underlie both the immunoassay cross-reactivity discussed in Chapter 6 and the metabolic relationship between methamphetamine and amphetamine discussed in Part IV.

Crystal structure

The form encountered medically and illicitly as a solid is methamphetamine hydrochloride, an ionic crystalline solid composed of protonated methamphetamine cations and chloride anions in a regular lattice. The macroscopic appearance depends on how the salt has crystallized: finely divided material appears as a white

powder, while slow crystallization can yield the coarse, translucent, glass-like crystals colloquially termed "ice," "crystal," or "glass." These differ in crystal habit and particle size, not in chemical identity — a coarse crystal and a fine powder of the same purity are the same substance. Crystalline form and particle size nonetheless matter analytically and forensically, because they influence dissolution, appearance-based presumptive judgments, and the homogeneity of a sample submitted for testing.

Solubility

Solubility is governed by the acid–base behavior described above. The **hydrochloride salt** is freely soluble in water, which is why it is the practical solid form for both pharmaceutical formulation and illicit distribution. The **free base**, by contrast, is an oily liquid that is poorly water-soluble but readily soluble in organic solvents. Because the molecule is a weak base, its distribution between aqueous and organic (or lipid) phases is pH-dependent: at high pH the un-ionized free base predominates and partitions into nonpolar phases and lipid membranes, whereas at low pH the protonated form predominates and remains in the aqueous phase. This single principle reappears throughout the book — it governs how analysts extract the drug from biological matrices (Chapter 6), how the drug crosses membranes and distributes in the body (Chapter 9), and how it behaves in environmental media (Chapter 27).

Stability

Methamphetamine is a comparatively stable small molecule. The hydrochloride salt is a stable crystalline solid under ordinary storage; the free base is volatile and will vaporize on heating well below the point of decomposition, behavior relevant both to its inhalational use and to its analysis by gas chromatography. The molecule can undergo photochemical and oxidative degradation under sufficiently harsh conditions, generating breakdown products, but it is robust enough to persist in stored forensic specimens and in environmental samples for extended periods — a durability that has consequences for the contamination of former production sites (Chapter 27) and for the retrospective analysis of biological evidence.

Its chemical robustness is, in a sense, part of why it is such a persistent public-health and environmental problem.

Spectroscopy

Every identification technique rests on a reproducible physical signature, and methamphetamine has several.

Mass spectrometry. Upon electron-impact ionization, methamphetamine fragments in a highly characteristic way. Cleavage adjacent to the nitrogen yields a dominant iminium fragment at mass-to-charge ratio (m/z) 58, which forms the base peak of the spectrum and is the single most diagnostic feature for identification; the molecular ion appears at m/z 149, with additional aromatic fragments at lower abundance. This fragmentation fingerprint, matched against reference libraries, is the basis of confirmatory mass-spectral identification.

Infrared (FTIR) and Raman. The molecule's vibrational spectrum — N–H and C–H stretches, aromatic ring modes, and a distinctive "fingerprint region" — provides an identifying pattern accessible to both infrared absorption (FTIR) and Raman scattering. Because portable FTIR and Raman instruments can capture this fingerprint quickly and without consuming the sample, they have become central to field identification and to community drug checking (Chapter 6).

Nuclear magnetic resonance (NMR). Proton NMR resolves the molecule's hydrogen environments — the five aromatic protons of the monosubstituted ring near 7.2–7.3 ppm, the methyl doublet of the side chain, the singlet of the *N*-methyl group, and the methine multiplet — yielding an unambiguous structural assignment. Quantitative NMR (qNMR) additionally allows purity determination against a reference standard, which is why NMR serves both as a confirmatory structural method and as a reference-laboratory tool for characterizing samples that simpler field methods cannot resolve.

Analytical Chemistry

How clinics, crime laboratories, and harm-reduction services actually identify methamphetamine — from rapid presumptive screens to definitive confirmation — and the well-documented pitfalls in between.

Analytical practice for methamphetamine is organized around a two-tier paradigm that recurs across clinical, forensic, workplace, and harm-reduction settings. A first tier of *screening* or *presumptive* tests is fast, inexpensive, and sensitive, but trades away specificity; a second tier of *confirmatory* tests is slower and costlier but definitive. The cardinal rule that follows from this structure — and the source of countless real-world errors when it is ignored — is that a positive screen is a presumption to be confirmed, never a conclusion in itself.

Immunoassays

Immunoassays are antibody-based tests that detect a target analyte by competition for antibody binding sites; they are the dominant screening technology in clinical and workplace urine testing and in many point-of-care devices, valued for speed, low cost, and ease of use. Their weakness is specificity. Because the antibodies recognize a structural motif rather than a unique molecule, amphetamine and methamphetamine immunoassays are notoriously prone to cross-reactivity with structurally similar compounds, producing false-positive screening results.

The list of documented cross-reactants is long and clinically important. It includes over-the-counter sympathomimetics such as **pseudoephedrine**, **ephedrine**, and **phenylephrine**;³ the antidepressant **bupropion**, whose metabolites can cross-react above roughly 500 ng/mL;⁴ the metabolite of **trazodone** (m-chlorophenylpiperazine); a metabolite of the antihypertensive **labetalol** that structurally resembles amphetamine;⁶ the antacid **ranitidine**; the lipid agent **fenofibrate**; the weight-loss drug **phentermine**; the antiparkinsonian **selegiline** (which is in fact metabolized to methamphetamine and amphetamine); and the related entactogens **MDMA**, **MDA**, and **MDEA**, among others.² A patient taking an ordinary decongestant or antidepressant can therefore screen positive for am-

phetamines while having taken no illicit drug at all. For this reason, clinical and forensic guidance is uniform: immunoassay results should not, on their own, support consequential decisions about employment, custody, clinical care, or organ donation.^{2,3}

Gas chromatography–mass spectrometry (GC-MS)

GC-MS is the long-standing confirmatory standard. It separates the components of a sample by gas chromatography and then identifies each by its electron-impact mass spectrum — for methamphetamine, the diagnostic m/z 58 base peak and molecular ion at m/z 149 described in Chapter 5 — matched against validated reference libraries. Because identification rests on a full, compound-specific fragmentation pattern after chromatographic separation, GC-MS is not subject to the cross-reactivity that bedevils immunoassays: where a positive screen is caused by a cross-reacting medication, confirmatory mass spectrometry simply does not confirm methamphetamine.² Confirmatory analysis frequently incorporates a derivatization step to improve chromatographic behavior and, importantly, to enable separation of the d- and l-enantiomers using a chiral derivatizing reagent — the analytical route to the enantiomer distinction discussed below.

Liquid chromatography–tandem mass spectrometry (LC-MS/MS)

LC-MS/MS has become increasingly central to clinical and forensic toxicology, complementing or replacing GC-MS in many laboratories. It pairs liquid chromatography with tandem mass spectrometry, monitoring specific precursor-to-product ion transitions to achieve very high sensitivity and specificity. Its advantages include excellent performance for polar analytes and metabolites, the ability to quantify many drugs in a single run, and reduced need for derivatization. In contemporary practice GC-MS and LC-MS/MS together constitute the confirmatory backbone for amphetamine-type stimulants.

Nuclear magnetic resonance (NMR)

NMR is less a routine clinical method than a reference-laboratory and seized-material technique. Its capacity for unambiguous structural assignment and, in quan-

titative mode, for purity determination makes it valuable both for confirming identity and for characterizing complex or novel samples. In drug-checking contexts it has a particular role: NMR (often alongside GC-MS or LC-MS) can identify novel psychoactive substances and adulterants that portable field instruments miss, and is sometimes used as the confirmatory reference against which field-method performance is judged.⁷

Infrared (FTIR) and Raman spectroscopy

FTIR and Raman are vibrational-spectroscopy methods that identify a substance by its molecular "fingerprint." Their great practical virtue is portability: handheld and benchtop ATR-FTIR and Raman instruments can identify the major components of a sample in minutes, without destroying it, and Raman can in some configurations scan through transparent packaging. Their limitations are equally important — they identify principally the major components and perform poorly at trace levels and in complex mixtures, so a potent adulterant present in small amounts may go undetected. These trade-offs make FTIR in particular the workhorse of point-of-care drug checking, paired with orthogonal methods to cover its blind spots.⁷

Drug-checking technologies

Drug checking — the analysis of illicit-market samples to inform the people who use them — has become a recognized harm-reduction strategy, operating in settings that range from music festivals to sanctioned community services and supervised-consumption sites across Europe, Australia, Canada, and, increasingly, the United States.^{7,9} Its purpose is twofold: to give an individual information about a specific sample, and to monitor the broader drug supply for emerging adulterants. It mirrors the laboratory's two-tier logic in a field-deployable form.

The typical technology stack combines a portable **FTIR spectrometer** — instruments such as the Bruker ALPHA or Agilent 4500a are widely used — with **lateral-flow immunoassay test strips** at the point of care, backed by confirmatory **GC-MS, LC-MS, or NMR** at a partner laboratory for samples the field tools cannot resolve.^{7,9} **Fentanyl test strips** are run on samples to detect fentanyl and certain

analogs; they are inexpensive, highly sensitive, and easy to read, but they return only a binary result, they fail to detect some analogs (carfentanil and certain others), and they are subject to false positives at high concentrations of some non-opioid drugs — including methamphetamine, MDMA, and diphenhydramine, typically above about 1 mg/mL — an interference that services manage by analyzing samples in sufficient dilution.⁸ **Benzodiazepine** and, more recently, **xylazine** test strips extend the panel as the adulterant landscape shifts. The Drug Checking BC service in Canada, for example, has operated point-of-care checking using Bruker ALPHA FTIR spectrometers and BTNX immunoassay strips across more than a dozen community sites since October 2017, contributing both individual results and a longitudinal picture of the local supply.⁹ One of the most consequential findings to emerge from such services has been the documented presence of fentanyl in a portion of methamphetamine and cocaine samples — direct evidence of the polysubstance contamination that drives much contemporary overdose risk.¹⁰

Drug testing, cutoffs, and the enantiomer question

Workplace and clinical urine testing operate against defined threshold concentrations. Under the United States federal (HHS/SAMHSA) Mandatory Guidelines, the initial immunoassay cutoff for amphetamines is 500 ng/mL, with d-methamphetamine as the target analyte, and the confirmatory cutoff for both amphetamine and methamphetamine is 250 ng/mL.^{1,5} A crucial interpretive rule applies specifically to methamphetamine: to be reported positive, a specimen must contain not only methamphetamine at or above the cutoff but also its metabolite amphetamine at a concentration at or above 100 ng/mL, a requirement intended to distinguish genuine methamphetamine exposure from certain confounders.^{1,5}

The enantiomer distinction introduced in Chapters 2 and 5 has a direct forensic application here. Because illicit methamphetamine is typically the d-enantiomer while certain legitimate exposures yield the l-enantiomer — the l-methamphetamine of some over-the-counter nasal inhalers, or the methamphetamine produced metabolically from selegiline — *chiral* analysis that separates d- from l-methamphetamine can help a Medical Review Officer interpret an otherwise ambiguous positive. The federal guidelines *permit* such enantiomer testing as an interpretive aid but do not *require* it.^{1,5} This is a clean illustration of why the chem-

istry of Chapter 5 is not academic: a stereochemical detail determines whether a confirmed laboratory result reflects illicit use or a cold remedy.

Method	Tier	Strength	Key limitation
Im-munoas-say	Screening	Fast, cheap, sensitive; point-of-care	Cross-reactivity → false positives; not definitive
GC-MS	Confirma-tory	Definitive ID; enables chiral separation	Lab-based; often needs derivati-zation
LC-MS/MS	Confirma-tory	High sensitivity/speci-ficity; multi-analyte	Instrument cost and expertise
NMR	Confirma-tory / ref-erence	Unambiguous structure; purity (qNMR); finds NPS	Not a field method; specialized
FTIR / Ra-man	Presump-tive (field)	Portable, non-destruc-tive, rapid	Poor at trace levels and complex mixtures
Fentanyl / benzo strips	Presump-tive (field)	Cheap, sensitive, imme-diate	Binary only; misses some analogs; conc.-dependent false positives

Pharmaceutical Manufacturing — A Historical and Regulatory Overview

A chapter about regulation, quality, and the public-health contrast between a controlled medicine and an uncontrolled substance — deliberately, and entirely, without operational detail.

Scope of this chapter

Consistent with this book's fixed boundaries, the following pages treat pharmaceutical manufacturing as a *regulated activity* and a *public-health phenomenon*. They do not describe procedures, chemistry, reagents, equipment, or conditions for producing methamphetamine by any route, licensed or illicit. The licensed–illicit comparison that closes the chapter is drawn solely in terms of quality, oversight, contamination, danger, and consequence — never method.

Industrial pharmaceutical production

Where methamphetamine is produced as a medicine — in the United States, the branded product Desoxyn — it is manufactured as enantiopure dextromethamphetamine hydrochloride under the regime of current Good Manufacturing Practice (cGMP). What this means in practice is that the product is made to a defined, published specification: a pharmacopoeial monograph (in the United States, a United States Pharmacopeia monograph for methamphetamine hydrochloride) fixes the requirements for identity, assay (potency), and limits on related substances and residual solvents, and the manufacturer is obliged to demonstrate, batch by batch, that the material meets them.¹¹ The defining feature of a pharmaceutical, from the patient's standpoint, is therefore not merely that it is "pure" but that its identity, strength, and impurity profile are *known and documented*. A 5-milligram tablet contains 5 milligrams, within tightly specified tolerances, every time.

Quality control

The quality systems behind that guarantee are extensive. They encompass identity testing, quantitative potency assay, profiling and limitation of related substances and degradation products, control of residual solvents and elemental impurities, dissolution testing, and formal stability testing under internationally harmonized (ICH) conditions to establish shelf life and storage requirements. Each batch is governed by validated, documented processes and complete records. The contrast that matters for this book is not a contrast of recipes but of *knowledge*: a licensed product carries a documented certificate of its composition, whereas an illicit-market product carries none — its potency is unknown, its impurities unprofiled, and its contaminants unmonitored. The harms attributed to "methamphetamine" in later chapters are, again and again, inseparable from this absence of quality knowledge in the illicit supply.

Regulatory oversight

Two regulatory architectures govern a pharmaceutical controlled stimulant, and they operate in parallel. The first is the medicines-regulation system: in the United States, the Food and Drug Administration approves the product, sets labeling, and inspects manufacturing facilities for cGMP compliance. The second is the controlled-substances system: the Drug Enforcement Administration schedules methamphetamine (Schedule II, as established in Part II) and administers a "closed system" of registration, security, recordkeeping, and — distinctively for controlled substances — aggregate production quotas that cap the total quantity that may be lawfully manufactured.¹² Internationally, the framework of the United Nations drug-control conventions, monitored by the International Narcotics Control Board, governs licit manufacture and trade and imposes controls on the precursor chemicals associated with illicit production.¹² The combined effect of these systems is that licensed methamphetamine exists within a dense web of accountability — quantities tracked, facilities inspected, distribution documented end to end — which is exactly the web that illicit production exists to evade.

Differences between licensed and illicit production

The distinction between licensed pharmaceutical manufacturing and illicit production can be stated fully and usefully without a single operational detail, because the differences that matter to public health are not differences of technique.

Quality and dose certainty. A licensed product has a known, documented identity, potency, and impurity profile; an illicit product does not. The unpredictability of the illicit product — variable and unknown purity, from batch to batch and seller to seller — is itself a primary driver of harm, because a person cannot calibrate to a substance whose strength is unknown.

Contamination and adulteration. A licensed product is profiled and limited for impurities and contaminants; an illicit product may contain manufacturing residues, byproducts, diluents, and deliberate adulterants, including — as the drug-checking evidence in Chapter 6 documents — potent contaminants such as fentanyl that the consumer neither expects nor can detect unaided.

Danger to makers and communities. Licensed manufacture occurs in engineered, inspected facilities. Clandestine production, by contrast, has historically been associated with serious hazards to those nearby and to the environment — fire and explosion risk, toxic exposures, and persistent contamination of buildings and land that imposes costly and difficult remediation, a subject treated in its own right in Chapter 27. These are consequences of the unregulated context, described here as public-health facts rather than as anything resembling instruction.

Legal status and accountability. The licensed product exists within the closed, documented system described above; the illicit product exists precisely to operate outside it, with no accountability for what it contains or what it does to the people who obtain it.

The throughline of this chapter, and a recurring theme of the book, is therefore simple: much of what distinguishes a medicine from a street drug is not the molecule but the *system* around it — the knowledge, the oversight, and the accountability that convert a potent chemical into a controlled therapeutic agent, and whose absence leaves the same chemical an unpredictable hazard.

References — Part III

Listed in order of first citation within Part III. Numbering restarts each installment; on final assembly the reference apparatus is to be consolidated. Sources current as of 2026.

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End of Installment II — Part III (Chapters 5–7)

*Part IV — Pharmacology (Chapters 8–10: Pharmacodynamics, Pharmacokinetics,
Dose–Response)
continues the volume.*