Major Stages of Pharmaceutical Development (Small-Molecule Drugs & Biologics) Introduction Developing a new pharmaceutical (whether a traditional small-molecule drug or a biologic therapy) is a lengthy, high-risk, and highly regulated process. On average, it takes on the order of 10–15 years from initial discovery to bring a single new medicine to market [Ref. 1]. This timeline spans multiple stages – from preclinical research through Phase 1, 2, and 3 clinical trials, regulatory review, and into post-marketing surveillance (often called Phase 4). The endeavor is extremely costly (often $1–3 billion when accounting for all failures and capital costs [Ref. 1, 14]), and only a small fraction of candidate compounds will ever succeed. In fact, roughly 1 in 5,000–10,000 compounds that begin in discovery end up approved [Ref. 9]. Even once a molecule enters human trials, the overall chance of approval is only on the order of 10% (about 1 in 10) [Ref. 2], meaning ~90% of drug candidates fail at some point in development. These statistics underscore why pharmaceutical R&D is carefully staged and closely overseen by regulators like the U.S. Food and Drug Administration (FDA) and the EU's European Medicines Agency (EMA) to ensure that only safe and effective products reach patients. Below, we provide a detailed report on each major phase of drug development – Pre-Clinical, Phase 1, Phase 2, Phase 3, and Post-Marketing (Phase 4) – including typical durations, costs, and success probabilities. We also highlight the roles of the FDA and EMA at each step, how critical path factors and setbacks can impact the overall timeline, and special regulatory designations and expedited pathways (Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review in the U.S.; PRIME and Conditional Marketing Authorisation in the EU) that can modify the development process. Tables are included to summarize phase-wise timelines and investments, phase attrition/success rates, and key distinctions between FDA vs. EMA procedures. Overview of Drug Development Phases Drug development is often described as a pipeline of sequential phases, each with distinct goals and rigorous requirements (Figure 1 – conceptual illustration, not provided here). In broad strokes, a new therapeutic begins in discovery and preclinical research (laboratory and animal studies). If a lead candidate shows promise, it enters human testing with Phase 1 (safety-focused) trials, followed by Phase 2 (initial efficacy) and Phase 3 (large-scale confirmatory efficacy) trials [Ref. 7]. After successful Phase 3 results, a comprehensive dossier is submitted to regulators (an NDA or BLA in the U.S., or an MAA in Europe) for regulatory review and approval. Even after market launch, development continues with Phase 4/post-marketing surveillance to monitor safety and sometimes explore new uses. Table 1 summarizes the typical timeframes and costs associated with each major phase. Note that these values are averages and can vary widely by therapeutic area and specific product. For instance, complex biologics or drugs for chronic illnesses may require larger, longer trials (and thus higher costs) than, say, a short-course antibiotic.

Nonetheless, the general trend holds: costs and time commitments escalate dramatically in later phases (Phase 3 trials are by far the most expensive and lengthy), and each successive phase has fewer surviving candidates due to attrition. Table 1 – Typical Duration and Cost by Development Phase (averages and ranges across indications) | Development Phase | Primary Purpose | Typical Duration (years) [Ref. 6] | Approx. Out-of-Pocket Cost [Ref. 5, 10] | | :---------- | :---------- | :---------- | :---------- | | Pre-Clinical (Discovery & Lab Research) | Lab and animal studies to identify a safe, promising candidate. | ~3–6 years (discovery & preclinical) [Ref. 6] | ~$15–100 million (varies; includes in vitro & animal tests) [Ref. 10]. | | Phase 1 Clinical | First-in-human trials; assess safety & dosage in small group (usually healthy volunteers). | ~1–2 years [Ref. 6] | ~$20–30 million on average [Ref. 5, 10]. | | Phase 2 Clinical | Evaluate efficacy, dose optimization, and side effects in patients (proof-of-concept). | ~2–3 years [Ref. 6] | ~$50–80 million on average [Ref. 5, 10]. | | Phase 3 Clinical | Large-scale trials to confirm efficacy and monitor adverse effects in diverse patient populations. | ~3–5 years [Ref. 6] | ~$200–350 million on average [Ref. 5, 10] (can exceed $500M–$1B for extensive trials [Ref. 10]). | | Regulatory Review & Approval (FDA/EMA) | Agency review of all data; decision on approval. | ~0.5–2 years (review process) [Ref. 7] | ~$2–3 million (filing fees and process) [Ref. 10] (excluding cost of maintaining staff during review). | | Post-Marketing Surveillance (Phase 4) | Ongoing monitoring of safety in real-world use; additional studies (e.g. long-term outcomes). | Ongoing (years/decades post-approval) | Variable ($20–300+ million) [Ref. 10] for required Phase 4 studies, safety reporting, etc. | Sources: Industry averages from PhRMA, Tufts CSDD, Deloitte, as summarized in [Ref. 5] and HHS/ASPE report data [Ref. 5]. Duration estimates from BIO industry analysis [Ref. 6]. Actual timelines and costs vary by drug and therapeutic area. As shown above, Phase 3 is typically the most time-consuming and expensive step, often involving multiple global trials with hundreds or thousands of patients. By contrast, early phases involve fewer subjects and lower costs. It’s also important to note that these figures include only direct trial costs (“out-of-pocket” expenses). When one factors in the high failure rate (the cost of many failed compounds for each successful drug) and the cost of capital over a decade or more, the total investment per approved drug rises into the billions [Ref. 1, 14]. Next, we delve into each stage in detail, then discuss regulatory oversight and special pathways that can alter the journey. Pre-Clinical Development (Discovery & Nonclinical Testing)

Overview:

The pre-clinical stage encompasses all research before human trials. This includes drug discovery (identifying a therapeutic concept and lead compound) and nonclinical testing in labs and animal models to assess basic safety and biological activity. For small-molecule drugs, discovery might involve screening thousands of chemical compounds for a desired biological effect. For biologics (e.g., monoclonal antibodies, recombinant proteins, vaccines), it often involves biotechnological design such as engineering a molecule to target a disease mechanism. On average, the combined discovery and preclinical research period can take 4–7 years [Ref. 6], though this varies widely.

Objectives:

The key goals in pre-clinical development are to demonstrate initial efficacy signs and acceptable safety in vitro and in vivo. Companies perform studies to understand a compound's pharmacology (how it affects its target and the organism) and toxicology (ensure it's not overtly poisonous). Typically, a lead candidate will undergo testing in at least two animal species (rodents and non-rodents) to evaluate toxicity, per regulatory guidelines, before human exposure. By the end of this phase, developers aim to have evidence that the drug "is reasonably safe for initial use in humans" and shows potential therapeutic activity [Ref. 11].

Regulatory Milestone:

In the U.S., before human trials can start, a developer must file an Investigational New Drug (IND) application with the FDA. The IND submission includes all preclinical data (efficacy, toxicology, pharmacokinetics), manufacturing information, and the proposed clinical trial protocols. The FDA reviews the IND to ensure that human subjects will not be exposed to undue risk; if the FDA does not object within 30 days, the sponsor may proceed with the first clinical trial. Similarly, in the EU, sponsors must obtain approval from national regulatory authorities (and ethics committees) via a Clinical Trial Application (CTA) for each country where a trial will be conducted (the process is being centralized via the EMA's Clinical Trials Information System as of 2022). Both FDA and EMA provide guidance on the required preclinical tests (largely harmonized through ICH guidelines), ensuring that by the time a drug reaches human trials, there is sufficient evidence of safety to justify proceeding.

Investment:

Preclinical work requires significant investment in R&D infrastructure (medicinal chemistry, biology, animal facilities). As shown in Table 1, the cost of the preclinical

phase is typically on the order of tens of millions of dollars (estimated ~$15–100 million in direct costs) [Ref. 10]. This includes synthesizing or biologically producing the candidate, formulation development, in vitro studies, animal studies (which must follow Good Laboratory Practice standards), and often manufacturing scale-up preparations for clinical grade material. Importantly, this phase also has a steep attrition: many candidates are eliminated due to toxicity or lack of efficacy before ever reaching humans. Industry analyses often cite that for every ~5,000 compounds that enter preclinical testing, only ~5 make it to human trials [Ref. 9] – a reflection of rigorous filtering to avoid exposing humans to unsafe or ineffective agents.

Biologics vs. Small Molecules:

While the overall preclinical process is conceptually similar, biologics development often involves additional complexities in ensuring consistent biological production (cell lines, biotech manufacturing) and assessing immunogenicity (the potential for the biologic to trigger immune reactions). Moreover, biologics may require species-specific considerations (a human antibody might not cross-react in a normal animal model, necessitating use of transgenic animals or surrogate molecules). Regulatory authorities (FDA/EMA) work with sponsors to address these challenges, often via scientific advice meetings before IND/CTA filing. By the end of preclinical development, if all goes well, the sponsor has compiled a robust data package and receives the green light to begin testing the drug in humans – marking the transition to the clinical phase. Phase 1 Clinical Trials (Safety & Tolerability)

Purpose:

Phase 1 is the first stage of clinical (human) testing. The primary focus is safety – to characterize how the drug interacts with the human body and to determine a safe dosage range. Phase 1 trials are usually small, involving 20–100 healthy volunteers in the case of many small-molecule drugs [Ref. 15]. (For certain serious diseases like cancer or HIV, where it would be unethical to expose healthy people, Phase 1 may enroll a small number of patients instead.) Researchers closely monitor participants for adverse effects and gather pharmacokinetic data (how the drug is absorbed, distributed, metabolized, and excreted).

Typical Design:

Phase 1 trials often use an ascending dose design – a small cohort of volunteers receives a very low dose, and if no severe safety issues arise, the next cohort gets a higher dose,

and so on, to find the maximum tolerated dose. There are also Phase 1 subtypes: SAD/MAD (single-ascending dose, multiple-ascending dose studies) and sometimes food-effect studies, etc. For biologics, additional assessments like immunogenicity (antibody formation) begin in Phase 1.

Duration and Success Rate:

A Phase 1 trial typically lasts around several months up to ~2 years (including data analysis) depending on the number of dose cohorts and whether multiple Phase 1 studies are done [Ref. 6]. The majority of drug candidates successfully clear Phase 1 – about 60–75% of compounds move from Phase 1 to Phase 2 [Ref. 2]. (In quantitative terms, an industry analysis of ~7,500 development programs found 63% of Phase I trials succeeded in reaching Phase II [Ref. 2].) Failures in Phase 1 are usually due to unexpected toxicity or unacceptable pharmacokinetics. While Phase 1 is primarily about safety, sometimes early hints of efficacy are observed (especially in Phase 1 studies on patients for diseases like cancer).

Regulatory Oversight:

Before Phase 1 begins, the FDA must have allowed the IND to proceed (as noted earlier). Throughout Phase 1, the study must adhere to Good Clinical Practice (GCP) and is typically monitored by an independent ethics board (IRB in the U.S.). The FDA may inspect Phase 1 trial conduct or data if concerns arise. In the EU, Phase 1 requires an approved CTA per country; ethics committees and national agencies oversee it. Regulators are especially cautious at this first-in-human stage – any serious adverse event (e.g., unexpected organ toxicity) could lead to a clinical hold, pausing the trial until a safety investigation is resolved.

Cost:

Phase 1 trials are the least expensive clinical phase, but still nontrivial – on the order of $10–30 million in direct costs for an average program (see Table 1). They usually involve intensive monitoring and often hospital/inpatient settings for safety, which contribute to cost. According to one analysis, Phase 1 trials cost roughly $25 million on average [Ref. 10]. Many companies also conduct Phase 1 in specialized Phase 1 units or through contract research organizations to manage these studies efficiently. In summary, a successful Phase 1 establishes that the drug can be safely administered to humans at doses that yield useful drug levels. Once a tolerable dose range is identified and initial

safety profile is acceptable, the drug can progress to the next stage, where efficacy becomes the focus. Phase 2 Clinical Trials (Initial Efficacy & Dose Optimization)

Purpose:

Phase 2 is often called “proof of concept” or therapeutic exploratory phase. Here the goal is to evaluate efficacy of the drug in patients with the target condition, while continuing to monitor safety and refine the dose regimen. Phase 2 trials enroll a larger group of patients (typically dozens to a few hundred patients) who have the disease or condition of interest [Ref. 15]. These studies often include a control group (e.g., placebo or standard of care) for comparison, though they may still be relatively small.

Key Questions:

Phase 2 asks, “Does the drug show signs of working in patients?” and “What is the optimal dose?”. Often Phase 2 is divided into Phase 2a (exploratory, smaller study focusing on efficacy signals) and Phase 2b (larger dose-finding studies). Endpoints may be clinical outcomes or surrogate markers of the disease. Safety surveillance continues, as less common side effects could emerge in a larger population. By the end of Phase 2, developers aim to determine whether the drug’s benefit-risk profile warrants proceeding to the large, expensive Phase 3 trials. Many sponsors will meet with the FDA (End-of-Phase-2 meeting) or EMA scientific advice at this juncture to get agreement on Phase 3 trial design.

Duration and Success Rate:

A typical Phase 2 program lasts about 2–3 years (sometimes longer if multiple trials are run or if recruitment is challenging) [Ref. 6]. This phase has historically been a major attrition point. Roughly only 30–40% of drug candidates that enter Phase 2 will successfully demonstrate sufficient efficacy and safety to advance to Phase 3 [Ref. 2]. (BIO’s data showed only ~31% of compounds move from Phase II to Phase III on average [Ref. 2].) Failures in Phase 2 often occur because the drug simply doesn’t show the hoped-for efficacy in patients, or the optimal dose can’t achieve enough effect without toxicity. From a project management perspective, Phase 2 is critical: a “no-go” decision here can save a company from investing in a doomed Phase 3; a strong “go” signal can attract partnering or funding.

Design Considerations:

Phase 2 trials are usually randomized, controlled trials (unlike many Phase 1s). They may be blinded and use placebo control or an active comparator. Because they are smaller than Phase 3, Phase 2 trials sometimes are not powered to conclusively prove efficacy, but rather to observe a trend or signal. Adaptive designs are increasingly employed – for example, dose groups might be dropped or added based on interim analyses to find the sweet spot quickly.

Regulatory Interaction:

Regulators do not "approve" Phase 2 per se (trials proceed under the IND/CTA), but they pay close attention. FDA may request a meeting after Phase 2 to discuss Phase 3 plans. In Europe, sponsors often seek Scientific Advice from the EMA or national agencies on Phase 3 trial protocols to ensure they meet regulatory expectations. It's in Phase 2 that sponsors might also pursue special designations if applicable – for instance, if the drug is for a serious condition and shows promising early data, the sponsor might apply for Breakthrough Therapy designation with FDA or PRIME status with EMA (discussed later), which can shape Phase 3 by enabling more regulatory guidance and possibly streamlined development.

Cost:

Phase 2 trials are costlier than Phase 1 due to larger patient numbers and more complex data collection. On average, Phase 2 can cost in the range of $50–$100 million for a program [Ref. 5]. An estimate of ~$60–70 million is often cited as an average per compound in Phase 2 [Ref. 5, 10]. Costs depend on trial size and length – e.g., a Phase 2 for a chronic disease that requires measuring long-term outcomes might cost at the higher end. In summary, Phase 2 is the inflection point where a drug must prove it has real therapeutic potential. Success here, coupled with a manageable safety profile, paves the way to the definitive Phase 3 trials. Conversely, a failure or inconclusive result in Phase 2 often spells the end of development for that candidate (or at least a major reevaluation). Phase 3 Clinical Trials (Pivotal Confirmatory Trials)

Purpose:

Phase 3 is the pivotal stage of clinical development. The aim is to firmly establish the drug's efficacy and safety in a large, definitive trial (or trials) that can support a marketing approval. Phase 3 trials are typically much larger – often hundreds to thousands of patients, across multiple sites (often multinational) – and are usually designed to provide statistically robust evidence that the new drug is effective for the

intended indication and to further characterize its safety profile in a broader population [Ref. 15]. These trials often compare the new drug to the current standard of care or placebo in a randomized, controlled fashion.

Scope and Design:

Phase 3 trials are usually double-blind, randomized controlled trials (RCTs) with endpoints that are agreed upon by regulators as clinically meaningful (e.g., improved survival, reduced disease incidence, etc.). Often multiple Phase 3 studies are required (e.g., two independent trials showing benefit) depending on the disease and regulatory guidance. For common ailments, Phase 3 trials might enroll several thousand patients to detect moderate benefit and monitor safety. For rare diseases, Phase 3 might be smaller but still as robust as possible. The duration of Phase 3 can be several years – not just due to trial length (patients might be followed for 1–2 years or more), but also due to the complexity of enrolling many patients worldwide and analyzing large datasets. On average, Phase 3 takes around 3 to 5 years to complete [Ref. 6]. Some lengthy outcomes trials (e.g., cardiovascular studies) can run even longer, whereas trials for fast-acting indications (like acute infections) might be shorter. In BIO's analysis, the success rate in Phase 3 was about 58% (i.e., ~58% of drugs entering Phase III generate sufficient results to proceed to filing an approval application) [Ref. 2]. This indicates that many drugs that look good in Phase 2 still fail in Phase 3 – sometimes due to an inability to reproduce earlier efficacy, or rare safety issues emerging at scale.

Regulatory Expectations:

Regulators are closely engaged by Phase 3. Sponsors usually have agreement with FDA and/or EMA on the Phase 3 trial design beforehand (via End-of-Phase-2 meetings or Scientific Advice). Deviating from agreed endpoints or statistical plans can jeopardize approval. Both FDA and EMA may require that certain patient subpopulations be included (e.g., ethnic diversity, both genders) and that Good Clinical Practice standards are strictly followed. Data integrity is paramount – regulatory inspectors may audit trial sites to validate Phase 3 data credibility during the review process.

Outcome:

Upon completing Phase 3, the sponsoring company will analyze the data. If results confirm that the drug is effective and safe enough, this supports the submission of a marketing application (NDA/BLA to FDA or MAA to EMA). It's common for a sponsor to compile an extensive dossier (often 100,000+ pages of reports) during Phase 3 and

enter the regulatory submission preparation stage even before final results if interim data are promising. If Phase 3 fails (e.g., no efficacy advantage or unexpected harm), the development is usually discontinued, resulting in a major loss of the investment. Because Phase 3 is so expensive, companies will sometimes halt a trial early for futility if interim analyses show it's unlikely to meet its endpoints (conversely, sometimes trials are stopped early for ethical reasons if the benefit is overwhelmingly positive, offering the control group the new therapy sooner).

Cost and Scale:

Phase 3 is by far the costliest phase (see Table 1). A single large Phase 3 trial can cost hundreds of millions of dollars. An average figure is around $250–$350 million per program [Ref. 10], but it's not unusual for large programs (e.g., in cardiovascular disease or large outcome trials) to cost $500 million or more. Some sources note that certain Phase 3 programs have exceeded $1 billion in expenditures [Ref. 10]. Costs are driven by the need to enroll many patients (often across dozens of hospitals or clinics globally), long trial durations (multiple years of treatment and follow-up), and extensive data collection (labs, imaging, etc.), as well as often the need to manufacture large batches of the drug for trial use. Biologics in particular might incur high production costs for Phase 3 supply. Given the enormous investment and criticality, Phase 3 is often referred to as the "make-or-break" moment for a drug candidate. A success here means the drug is likely on the path to approval. A failure can mean the end of the line (though in some cases, a partial success might lead to a narrower indication or an additional trial). Before moving on to the regulatory filing stage, it's worth examining the overall probability of success across phases. Table 2 provides a summary of typical success rates at each transition (based on large analyses of industry data): Table 2 – Probability of Success by Phase (Clinical Development Attrition) | Stage of Development | Probability of Advancing to Next Phase [Ref. 2] | Approx. Probability of Ultimate Approval (if in this phase) [Ref. 2, 8] | | :---------- | :---------- | :---------- | | Preclinical to Phase 1 | ~10% (from lead discovery to human trials, very low due to high early attrition) | ~? (Few %; historically ~5 out of 5,000 compounds reach humans [Ref. 9]) | | Phase 1 to Phase 2 | ~63% succeed in Phase 1 and enter Phase 2 [Ref. 2]. | ~10% chance of eventual approval from Phase 1 start [Ref. 2] (i.e., ~9.6%, industry-wide). | | Phase 2 to Phase 3 | ~31% of drugs move from Phase 2 to Phase 3 [Ref. 2]. | ~15–20% chance of eventual approval if already in Phase 2 (varies by indication). | | Phase 3 to NDA/BLA Submission | ~58% of drugs advance from Phase 3 to filing an application [Ref. 2]. | ~50% chance of approval if currently in Phase 3. (Roughly half of Phase 3 candidates will gain approval.) | | Regulatory Approval

(NDA/BLA filing to approval) | ~85% of filed applications are approved [Ref. 2]. (Others receive rejection or requests for more data.) | ~85% chance of approval once an application is submitted (for drugs that made it this far). | Sources: Large-scale analysis by BIO/BioMedTracker of 2006–2015 programs [Ref. 2], which found an overall ~9.6% success from Phase 1 to approval. PhRMA similarly reports ~12% of new molecular entities entering clinical trials win FDA approval [Ref. 1]. Success probabilities vary by therapeutic area (e.g., oncology projects have lower success rates, ~5%, whereas some others like infectious diseases are higher) [Ref. 8]. The funnel of attrition is evident: thousands of candidates to get one approved drug, and even after human trials start, roughly 1 in 10 will succeed. These statistics highlight the risk at each stage. They also inform portfolio management in pharmaceutical companies – e.g., knowing that only ~1/3 of Phase 2 drugs will reach Phase 3 encourages robust stage-gate decisions and often over-subscription of Phase 1 projects expecting later attrition. With Phase 3 completed successfully, the next step is to seek regulatory approval to actually market the drug. Regulatory Review and Approval (FDA & EMA Processes) After a successful Phase 3 (or sometimes based on Phase 2 for accelerated programs), the company must compile all evidence into a regulatory submission to seek marketing authorization. This stage is essentially the critical evaluation by regulators of whether the drug can be allowed on the market for doctors to prescribe. The process and nomenclature differ slightly between the U.S. FDA and the European system via EMA, but the core principles are similar: the data must convincingly demonstrate the drug's quality, safety, and efficacy for its intended use, and that the benefits outweigh the risks. U.S. – FDA Approval Process: For the U.S. market, the company submits a New Drug Application (NDA) for small-molecule drugs or a Biologics License Application (BLA) for biologics to the FDA's Center for Drug Evaluation and Research (CDER) or Center for Biologics (CBER) as appropriate. This application contains the full reports of all preclinical and clinical studies, manufacturing details (CMC – Chemistry, Manufacturing, and Controls), proposed labeling, and more. The FDA first conducts a 60-day preliminary review to ensure the application is complete (this is the filing or validation step) [Ref. 11]. Once accepted ("filed"), the NDA/BLA enters formal review. The FDA's standard review timeline under the Prescription Drug User Fee Act (PDUFA) is 10 months from filing for a standard review, or 6 months if the drug is granted Priority Review designation (more on this expedited designation below). During this time, FDA assembles a multidisciplinary team (medical officers, pharmacologists, statisticians, chemists, etc.) to evaluate the data. They may ask the sponsor questions or request additional analyses; often there is an interactive back-and-forth. FDA may also convene an advisory committee meeting – an independent panel of experts – to publicly discuss the application and seek advice on complex issues (common for novel drugs or

those with safety concerns). At the end of the review, FDA will issue either an approval (if criteria are met) or a Complete Response Letter (CRL) if there are deficiencies [Ref. 11]. An approval means the product can be marketed in the U.S. for the approved indication, with agreed label (prescribing information). A CRL outlines issues (insufficient evidence of efficacy, safety concerns, manufacturing problems, etc.) that preclude approval; the sponsor must address these (which could mean additional studies or analyses) and resubmit. About 85–90% of NDAs/BLAs that get filed and undergo full review eventually get approved [Ref. 2], although sometimes not on the first pass (some receive a CRL and then are approved in a subsequent submission after additional data). Europe – EMA Approval Process: In the European Union, pharmaceutical approvals for innovative medicines are typically through the Centralised Procedure coordinated by the EMA. The company submits a Marketing Authorisation Application (MAA) to the EMA. The EMA's Committee for Medicinal Products for Human Use (CHMP) – a scientific committee with representatives from each EU member state – conducts the scientific assessment of the MAA [Ref. 12]. The evaluation process under the centralised procedure is officially 210 days of active review time [Ref. 4], but this clock is often paused ("clock stop") to allow the sponsor to respond to questions partway (commonly at Day 120 and Day 180 of review). In practice, a standard EMA review typically takes around 12–15 months from submission to decision, similar to FDA's timeframe [Ref. 6, 13]. At the end, the CHMP will adopt a scientific opinion on whether the drug should be approved [Ref. 12]. This opinion is then sent to the European Commission, which by law makes the final decision and grants the marketing authorisation valid across the EU (and EEA countries) [Ref. 12]. The European Commission usually makes a final legally binding decision within 67 days of receiving a positive CHMP opinion [Ref. 12]. (This step is largely administrative but is a notable procedural difference: the FDA itself issues approvals in the U.S., whereas in the EU the EMA recommends and the European Commission formally authorizes the product [Ref. 12, 13].) One practical effect of this is timing differences: historically, the FDA has often approved drugs a few months faster than the EMA, partly because the FDA can start reviews sooner (companies often apply to FDA first) and because the EMA's additional Commission step adds ~2 months [Ref. 13]. Studies comparing 2010s approvals found the median lag between FDA and EMA approval for the same drugs was a few months, though this gap has narrowed in recent years [Ref. 13].

Review Criteria:

Both FDA and EMA require robust evidence of efficacy from well-controlled trials and a demonstration of safety. The standards are fundamentally similar due to international harmonization (ICH guidelines). However, there are subtle differences in emphasis and

process. For example, EMA's review will include input from the PRAC (Pharmacovigilance Risk Assessment Committee) specifically on the drug's risk management plan [Ref. 12], and if the product is an advanced therapy (gene or cell therapy), the CAT (Committee for Advanced Therapies) also gives an opinion [Ref. 12]. The FDA doesn't have an exact analogue of those committees but handles such issues within review divisions or advisory committees.

Biologics Considerations:

Biologics in the U.S. go through a BLA but the process and timeline are effectively the same as NDAs (the difference is mainly legal/regulatory pathway – Public Health Service Act for BLAs vs. Food, Drug, and Cosmetic Act for NDAs). In the EU, biologics (if they are within scope of the centralised procedure, which most are) go via EMA as well – in fact the centralised procedure is mandatory for biotech-derived products, ensuring a single EU-wide approval. At the end of this rigorous review, if the outcome is positive, the drug is approved for marketing. The company can then launch the product, and doctors can prescribe it for patients. Approval also comes with post-marketing conditions (see next section) and, for certain drugs, requirements like Risk Evaluation and Mitigation Strategies (REMS) in the U.S. or additional monitoring (▼ label in EU indicating extra pharmacovigilance). It is worth summarizing some key differences between FDA and EMA procedures, which we do in Table 3 below: Table 3 – Comparison of FDA vs. EMA Regulatory Processes | Aspect | FDA (United States) | EMA (European Union) | | :---------- | :---------- | :---------- | | Regulatory Authority | U.S. Food and Drug Administration – a single national agency. | European Medicines Agency – a coordinating agency (scientific evaluations via CHMP), with final approval by the European Commission [Ref. 12, 13]. | | Application Type | NDA (New Drug Application) for small molecules; BLA (Biologics License Application) for biologics. | MAA (Marketing Authorisation Application) for all human medicines (biologics and small molecules alike) under centralised procedure. | | Review Timeline (Standard) | ~10 months review time (from filing) for standard applications. (Plus a 60-day initial filing review) [Ref. 7]. | ~210 days active review for CHMP [Ref. 4] + "clock stops" for questions; ~12–15 months total. European Commission decision adds ~67 days [Ref. 12]. | | Decision Authority | FDA itself grants the approval (CDER/CBER directors sign off). | CHMP gives a recommendation; the European Commission issues the legally binding authorisation valid in all EU/EEA countries [Ref. 12]. | | Advisory Committees | Frequently uses independent Advisory Committee meetings for expert input on approvals (especially novel or risky drugs). Advisory vote is not binding but influential. | No external ad-hoc committees; instead, CHMP members (from member states) are the

experts. However, CHMP may enlist additional experts or hold public hearings in special cases. | | Post-Approval Measures | FDA can require Phase 4 studies or REMS programs for safety. Monitors adverse events via FDA's MedWatch/FAERS. Periodic safety updates required. | EMA/Commission may grant approval with specific obligations (e.g., under conditional approval) or require PASS (post-authorisation safety studies). Monitors via EudraVigilance, with PRAC oversight. | | Expedited Programs | Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, etc., to speed development/review of qualifying drugs [Ref. 3]. | PRIME scheme, Accelerated Assessment, Conditional Marketing Authorisation, etc., for promising or needed medicines (analogous concepts to US programs) [Ref. 4]. | | Scope of Authorization | Approval is for U.S. market only (FDA does not directly confer approval elsewhere). | Centralised EMA approval is pan-European (valid in 27 EU member states plus EEA countries) [Ref. 12]. (National approvals exist for some drug types not in central procedure scope.) | Sources: FDA and EMA official guidance [Ref. 3, 4, 11, 12]; comparative analyses [Ref. 13]. Despite procedural differences, FDA and EMA often align closely in their judgments – studies show a high concordance (90%+ agreement on decisions) between the two agencies [Ref. 13]. However, timing can differ and occasionally one agency may approve a drug that the other rejects or asks for more data on. For a global pharmaceutical company, navigating both FDA and EMA requirements in parallel is a critical task, and usually filings are done in both jurisdictions (and others like Japan) around the same timeframe to maximize the drug's global reach. Post-Marketing Surveillance (Phase 4) Approval is not the end of the story. Once a drug is on the market and used in a much larger population, ongoing surveillance is essential to ensure continued safety (and to gather real-world effectiveness data). This stage is commonly referred to as Phase 4 or post-marketing. Its scope includes all activities and studies after a drug is marketed: Adverse Event Monitoring: Both FDA and EMA have systems for collecting reports of adverse drug reactions from healthcare professionals and patients. In the U.S., the FDA's FAERS database (FDA Adverse Event Reporting System) accumulates reports. In the EU, EudraVigilance does similarly across member states. Companies are legally required to pharmacovigilance reporting – they must promptly report serious unexpected adverse events and submit periodic safety update reports. Regulatory authorities assess these and can take actions (up to and including withdrawing a drug or updating warnings) if new risks emerge. Phase 4 Studies: Often, regulators require specific post-marketing studies as a condition of approval. For drugs approved via Accelerated Approval (FDA) or Conditional MA (EMA), the sponsor must conduct confirmatory trials (usually ongoing or new Phase 3 studies) to verify the clinical benefit since the initial approval was on surrogate endpoints [Ref. 11]. Other Phase 4 commitments might include studies in special populations (e.g., pediatric

studies, if the drug was initially approved for adults, or vice versa), or long-term safety studies. According to one estimate, post-marketing study commitments can cost anywhere from tens of millions up to a few hundred million dollars depending on their size and scope [Ref. 10]. Lifecycle Management: Companies may also undertake additional Phase 4 trials not just for safety, but to explore new indications, new dosing regimens, or combinations. While not mandated, these can expand the drug's market usage (for instance, a cancer drug initially approved for late-stage disease might be tested in earlier-stage disease in Phase 4). From a regulatory standpoint, if a company finds a significantly new benefit or use, they would submit a supplemental application for a new indication. Risk Management: Both FDA and EMA employ risk management plans. FDA's REMS (Risk Evaluation and Mitigation Strategies) might require specific measures (like prescriber training, patient registries, or restricted distribution) after approval for certain drugs with serious risks. EMA similarly requires a Risk Management Plan (RMP) for every drug, which could include additional pharmacovigilance or risk minimization measures in the EU. These plans are monitored in Phase 4. The post-marketing phase is indefinite – as long as a drug is on the market, safety surveillance continues. Many safety issues (especially rare side effects) only become apparent when hundreds of thousands of patients use a drug, which is why robust Phase 4 is crucial. A historical example is the withdrawal of rofecoxib (Vioxx) after post-market studies revealed cardiovascular risk that wasn't fully appreciated in pre-approval trials. Regulators can and do sometimes update labeling (package inserts) with new warnings, contraindications, or dosage adjustments as evidence from Phase 4 accumulates. From the patient and healthcare perspective, Phase 4 is about ensuring the drug is used appropriately and remains more beneficial than harmful in the real world. For regulators, it's an extension of their mission to safeguard public health beyond the approval event. Critical Path in Development & Impact of Delays/Successes Drug development is often described in project management terms, where each phase's outcome determines the next steps. The critical path refers to the sequence of tasks that determine the overall project duration. In pharmaceutical R&D, the critical path typically runs through the longest and most essential experiments – usually the clinical trials, especially Phase 3. Factors that affect these critical path activities can significantly alter the overall timeline: Patient Recruitment and Trial Length: Enrollment of patients is frequently the rate-limiting step. Delays in recruiting participants for a trial (due to a rare disease population, competition with other trials, etc.) will push timelines out. For example, a Phase 3 trial projected for 3 years might take 4 if enrollment is slower than expected. Success in speeding enrollment (perhaps by opening more sites or expanding inclusion criteria) can accelerate completion. Interim Results and Early Stopping: Occasionally, a trial can be stopped early for

overwhelming efficacy – if interim data shows the drug works so well that it would be unethical to continue placebo, trials may conclude sooner, potentially allowing an earlier submission (this is a “success” scenario impacting timeline positively). Conversely, stopping early for futility (recognizing a trial is unlikely to meet endpoints) can save time and resources that would have been wasted, effectively cutting losses. Parallelization of Activities: Companies often run certain activities in parallel to shorten the critical path. For instance, sometimes Phase 2b and Phase 3 might overlap or a company might start manufacturing scale-up during Phase 3 rather than waiting for approval. These decisions carry risk (investing before certainty of approval) but can shave time off the path to launch if successful. Regulatory rolling review (as in Fast Track designation) can also parallelize some review steps (the FDA will review portions of the application before the full NDA is submitted), thus shortening the post-trial timeline [Ref. 3]. Setbacks Needing Additional Trials: If a Phase 3 trial yields ambiguous results, regulators might not approve without an extra study. This is a scenario where a delay cascades: instead of approval, the company must perhaps run a Phase 3b or additional Phase 3 trial to satisfy concerns, adding years. Similarly, manufacturing or quality issues (e.g., inability to consistently produce the biologic at scale) can delay regulatory approval until resolved. Breakthroughs and Expedited Pathways: Obtaining a Breakthrough Therapy designation from FDA or PRIME from EMA can significantly impact timeline. These programs aim to compress development by increasing guidance and interaction – for a breakthrough-designated drug, FDA actively works with the sponsor on the most efficient trial design, sometimes allowing a combined Phase 2/3 trial or fewer total trials if the evidence is strong [Ref. 3]. This can cut years off the development path. Likewise, Accelerated Approval can allow marketing earlier (after Phase 2) with confirmatory trials happening post-approval, effectively moving part of the critical path to the post-market space and giving patients earlier access [Ref. 3]. Regulatory Review Shortcuts: Programs like Priority Review (FDA) and Accelerated Assessment (EMA) shorten the review timeline (from ~10 to 6 months at FDA; 210 to 150 days at EMA) [Ref. 3, 4]. While these don’t affect the clinical trial timeline, they do truncate the time from final data submission to decision, which can be critical for patients awaiting new therapies. In project terms, they shorten the final critical path segment (regulatory approval). Failures Early vs. Late: If a drug is destined to fail, an early failure (e.g., failing fast in Phase 1 or 2) actually prevents wasted time on the critical path. That frees resources to pursue other projects. A late failure in Phase 3 is most costly time-wise (often 8–10 years may have been spent). This is why robust interim assessments and go/no-go criteria at Phase 2 are important; success there needs to be reasonably predictive of Phase 3 success to commit to Phase 3. Sometimes, adaptive Phase 3 designs allow an interim look to possibly stop for

futility and avoid further delay. In sum, the overall 10-15 year timeline can be visualized as a series of dependent steps, and any bottleneck or acceleration in one step propagates forward. Companies and regulators have put significant effort into initiatives to "optimize the critical path" – for example, the FDA's Critical Path Initiative launched in the 2000s sought new scientific tools to streamline development. The emergence of platform trial designs, use of surrogate endpoints, better biomarkers, and digital technology for recruitment are all modern efforts to reduce unnecessary delays in development while still gathering the evidence needed for a decision. Perhaps the most striking recent illustration of critical path compression was the development of COVID-19 vaccines in 2020: companies and regulators overlapped phases (e.g., starting Phase 3 before Phase 2 was fully complete), used rolling reviews, and took on manufacturing scale-up at risk, achieving approval in under a year [Ref. 1] – an unprecedented acceleration, albeit under exceptional circumstances and with substantial prior scientific groundwork. For a more typical program, each phase's outcome dictates the next, and careful planning (plus some luck in trial results) is needed to keep the project on track. Delays can come from scientific challenges, operational issues, or regulatory requests; successes, especially those recognized via expedited pathways, can shorten the journey to patients. Special Regulatory Designations & Expedited Pathways Both the FDA and EMA have established programs to expedite development and review for medicines that address serious conditions or unmet medical needs. These programs are crucial for getting important therapies to patients faster by removing some hurdles or providing more support/guidance. Below we outline the key designations mentioned (Fast Track, Breakthrough, Accelerated Approval, Priority Review in the U.S.; PRIME and Conditional Approval in EU), along with their meanings and impacts: Fast Track (FDA): Purpose: Facilitates development and expedites review of drugs for serious conditions with unmet medical need. Benefits: Enables more frequent meetings with FDA, more frequent written correspondence, and importantly rolling review of the NDA/BLA (the company can submit portions of the application, such as clinical data, for FDA review before the full application is complete) [Ref. 3]. This can speed up the review process overall. Fast Track does not change the standard for approval or automatically confer priority review, but drugs on Fast Track can be considered for Priority Review if criteria met. Example: Many new antivirals for serious diseases, or therapies for rare serious diseases, get Fast Track status to help coordinate their development with FDA early. Breakthrough Therapy (FDA): Purpose: Expedite development and review of a drug that may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints [Ref. 3]. It's for serious or life-threatening conditions with preliminary clinical evidence of a dramatically improved effect. Benefits: FDA provides intensive guidance and

organizational commitment (involvement of senior managers) to help the sponsor design efficient trials – often potentially merging phases or minimizing the total number of patients needed by optimizing trial design. A Breakthrough therapy also automatically qualifies for Fast Track benefits (rolling review) and usually for Priority Review of the NDA. Example: Has been used, for example, in oncology drugs showing very high response rates in early trials, to speed them to market. Breakthrough designation signals FDA's strong belief that the drug is promising, and indeed these drugs often get to approval substantially faster than average (sometimes in ~4–5 years from Phase 1 to approval, vs. ~10 normally). Accelerated Approval (FDA): Purpose: Allows early approval based on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit [Ref. 3]. This program (codified in 1992) is targeted at serious conditions with unmet need. Benefits: Gets drug to market sooner (often using Phase 2 results for approval). Catch: The sponsor must conduct post-approval confirmatory trials to verify the anticipated clinical benefit; if those trials fail to confirm benefit, FDA has authority to withdraw the drug. Example: Extensively used in oncology, HIV, etc. Many HIV antivirals in the 90s were approved on surrogate endpoints (CD4 counts or viral load) and confirmed later. Priority Review (FDA): Purpose: This is a designation for the NDA/BLA review phase (granted at time of filing or during review) indicating the drug is for a serious condition and would provide a significant improvement in safety or effectiveness, or meets other priority criteria (e.g., a pediatric priority). Benefits: If granted, FDA shortens the target review timeframe to 6 months instead of the standard 10 months [Ref. 3]. Priority Review does not affect the clinical trial requirements, only the speed of FDA's review. Impact: Can reduce time to approval by ~4 months, which for life-threatening diseases can be meaningful. The FDA's goal is to take action (approve or issue a CRL) within this 6-month window. Over at the EMA, we have analogous concepts: PRIME (PRIority MEdicines) – EMA: Purpose: Launched in 2016, PRIME is a scheme to enhance support for the development of medicines that target an unmet medical need and show potential to offer a major therapeutic advantage based on early data [Ref. 4]. It's essentially the EMA's version of Breakthrough Therapy designation. Benefits: If a drug is accepted into PRIME, the sponsor benefits from early and enhanced interaction with EMA experts during development. This includes kick-off meetings to discuss development plan, assignment of a rapporteur from CHMP for continuous support, and the promise of accelerated assessment at the time of MAA (see below). Like FDA's breakthrough, the goal is to help promising drugs get through trials faster by optimizing design and ensuring regulatory requirements are understood early. To qualify, preliminary clinical data (often Phase 1 or 2) should suggest the drug is a game-changer for patients with no good options [Ref. 4]. Example: PRIME has been granted to certain advanced therapy

medicinal products (ATMPs) like gene therapies for rare diseases, where early signs are very promising. Accelerated Assessment (EMA): Purpose: This is the EMA's counterpart to Priority Review. If granted (typically for medicines of major public health interest, e.g., breakthrough innovation or urgent need), the EMA targets a 150-day review by CHMP instead of the standard 210 days [Ref. 4]. Benefits: Can shorten the EMA process by a few months (though companies still need to address questions during the process). Accelerated assessment is often given to PRIME-designated medicines at submission, assuming the data indeed shows the high benefit. It is requested at time of filing the MAA and CHMP decides whether criteria are met. Note: Accelerated assessment doesn't lower evidence requirements, just speeds the evaluation process. Conditional Marketing Authorisation (EMA): Purpose: This pathway (introduced 2006) allows the EMA to grant a marketing approval on the basis of less complete data than normally required, if the medicine addresses a serious condition, unmet need, and the benefit of immediate availability outweighs the risk of having less data [Ref. 12]. Conditions: It is "conditional" on the sponsor completing specific post-approval studies to provide the comprehensive data (similar spirit to FDA's Accelerated Approval). The approval under this route is valid for one year at a time and is renewable; it's meant to facilitate early access for patients in dire need while confirmatory trials are still ongoing [Ref. 12]. Example: Conditional approvals have been used for certain oncology drugs, or medicines for emergencies (e.g., during public health crises) where waiting for full long-term data would delay access. About 20–25% of orphan drugs in EU have been approved via conditional approvals in the last decade [Ref. 12]. If the obligations are fulfilled and data confirms benefit, the status can be converted to a "normal" full approval. Exceptional Circumstances (EMA): (Not explicitly asked, but for completeness) EMA can grant an approval in exceptional circumstances when comprehensive data can't be obtained at all (perhaps due to extreme rarity of disease or ethical constraints). This is a somewhat rarely used path where conditions are imposed for safety monitoring but no expectation that all usual data will ever be available. Both FDA and EMA also have Orphan Drug designation programs (for rare diseases) which provide incentives like fee waivers and market exclusivity; while not directly an "expedited approval" pathway, orphan designation often coincides with use of some expedited programs for serious rare conditions. Another FDA program, RMAT (Regenerative Medicine Advanced Therapy), exists specifically for cell/gene therapies and is analogous to Breakthrough but for regenerative meds [Ref. 3]. It's helpful to see how these expedited pathways compare between FDA and EMA: FDA Priority Review vs. EMA Accelerated Assessment: Both shorten the review clock (6 months vs. 10, and 150 days vs. 210) [Ref. 3, 4]. FDA Accelerated Approval vs. EMA Conditional Approval: Both allow early approval based

on surrogate endpoints with post-market obligations [Ref. 3, 12]. FDA Fast Track & Breakthrough vs. EMA PRIME: These are about expediting development (e.g., more guidance, trial design help) and eligibility for speedy reviews [Ref. 3, 4]. Breakthrough is more intensive than Fast Track. EMA's PRIME is conceptually similar to Breakthrough (high-level support for especially promising drugs). Other: FDA also has Emergency Use Authorizations (EUA) for emergency situations (like pandemics) – not a standard development pathway, but a regulatory tool for crises. EMA has equivalents like conditional approvals used in emergencies (e.g., COVID-19 vaccines in EU were given conditional marketing authorisations in 2020 based on limited data, with commitments for more). These designations significantly affect the critical path of development. For example, a Breakthrough therapy might reach the market in a fraction of the time because Phase 3 requirements could be reduced or trial protocols optimized with FDA's input, and review is faster. Table 4 (below) provides a quick reference of these expedited programs: Table 4 – Selected Expedited Pathways: FDA vs EMA | Expedited Program | FDA (U.S.) – Definition & Benefit | EMA (EU) – Definition & Benefit | | :---------- | :---------- | :---------- | | Fast Track | For serious unmet needs; enables frequent FDA interaction and rolling submission [Ref. 3]. Aims to speed development & review. | (No exact equivalent name; PRIME/accelerated assessment cover similar intent.) Sponsors can seek Scientific Advice at EMA at early stage; no rolling review per se in EU, but flexible early interaction via PRIME. | | Breakthrough Therapy | For drugs with early evidence of substantial improvement on clinical endpoints vs. existing therapies [Ref. 3]. FDA provides intensive guidance, organizational commitment; includes Fast Track benefits (rolling review). Greatly streamlines development. | PRIME (PRIority MEdicines): For promising drugs addressing unmet need with major advantage (based on early data) [Ref. 4]. EMA provides early support, enhanced guidance, and eligibility for accelerated assessment at MAA. Similar in spirit to Breakthrough. | | Accelerated Approval | Allows approval based on surrogate endpoints for serious conditions [Ref. 3]. Gets drug to market sooner; post-approval confirmatory trials required to verify benefit. Used often in oncology, rare diseases. | Conditional Marketing Authorisation: Allows approval with incomplete data if unmet need [Ref. 12]. Drug can be marketed with "conditional" status; company must complete studies post-approval. Annual renewal until full data. Ensures earlier patient access in return for data commitments. | | Priority Review | FDA will aim to decide on application in 6 months (instead of 10). Granted for therapies with significant benefit or addressing unmet needs. Shortens time to approval decision. | Accelerated Assessment: CHMP review in 150 days (instead of 210) for drugs of major interest [Ref. 4]. Granted for innovative or urgent-need medicines (often those with

PRIME status). Speeds up EU decision by ~60 days. | | Other Notes | FDA also has Orphan Drug (7-year exclusivity + fee waivers for rare diseases), RMAT for regenerative medicine (similar to Breakthrough), and Emergency Use Authorization (EUA) for crises. | EMA has Orphan status (10-year exclusivity in EU for rare diseases) and can use exceptional circumstances or compassionate use programs for special cases. The EU-U.S. designations often overlap (e.g., a product can be both Breakthrough (FDA) and PRIME (EMA)). | Sources: FDA and EMA official guidance [Ref. 3, 4, 11, 12]; comparative analyses [Ref. 13]. These mechanisms underscore regulators' flexibility in advancing critical therapies. They are carefully applied – e.g., Breakthrough designation requires convincing early data, and Conditional approvals in EU are used sparingly when benefit justifies uncertainty. Importantly, none of these lower the standards of evidence for final approval; rather, they allow earlier decisions or more efficient evidence gathering. For instance, even under Accelerated Approval/Conditional Approval, if the follow-up trials do not confirm the expected benefit, the drug can be pulled from the market [Ref. 11]. From a strategic viewpoint, companies will often pursue these designations as early as possible for qualifying drugs, since they can substantially reduce development time and cost. Patients benefit by getting faster access to innovative treatments (e.g., certain breakthrough oncology drugs reaching market years sooner than traditional pathways would have allowed).

Conclusion Pharmaceutical development is a complex, multi-phase endeavor that balances scientific rigor with patient urgency. Each stage – from the laboratory bench in preclinical research, through each phase of clinical trials, to the detailed scrutiny of regulatory review – is critical to ensuring that by the time a drug reaches the public, it is both safe and effective for its intended use. For professionals coming from other regulated industries, the drug development process may appear long and costly, but it is the product of decades of learned lessons in safeguarding patient health. Major regulatory authorities like the FDA and EMA serve as gatekeepers and guides in this journey, with their regulations, guidances, and oversight shaping every phase. They not only enforce standards but also provide pathways to accelerate development when public health demands it and the science is compelling. In summary, the major stages of drug development – Pre-Clinical, Phase 1, Phase 2, Phase 3, and Post-Marketing – form a pipeline with steep hurdles at each juncture. The timeframes (often a decade or more) and investments (often billions of dollars) reflect the difficulty of translating a biomedical idea into a safe, marketable therapy. Nevertheless, modern approaches and expedited programs are improving efficiency: today, targeted therapies and critical vaccines have made it to patients faster than ever thought possible, thanks to Breakthrough designations, rolling reviews, and global regulatory collaboration. Understanding this process in detail is essential for anyone entering the pharmaceutical

sector. It not only illuminates why bringing a new drug to market is so challenging, but also highlights the remarkable coordination of science, regulation, and medicine required to deliver new cures and treatments to the people who need them. References PhRMA (Pharmaceutical Research and Manufacturers of America). “Research & Development: Drug Development Process.” PhRMA Fact Sheet. (It takes 10–15 years and costs $2.6B on average to develop a new medicine; only ~12% of compounds entering clinical trials are approved). Biotechnology Innovation Organization (BIO) et al., “Clinical Development Success Rates 2006–2015.” (Industry study analyzing 7,455 development programs; found overall 9.6% Phase I-to-approval success, with Phase transition probabilities ~63% Phase1→2, 31% Phase2→3, 58% Phase3→NDA, and 85% NDA→approval). FDA – “Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review.” (FDA overview of expedited programs for serious conditions). EMA – “EMA PRIME and Accelerated Assessment.” (EMA guidance on PRIME designation and accelerated review timelines; CHMP assessment is 210 days standard or 150 days accelerated). U.S. Dept. of Health and Human Services, ASPE Report (2022). “Development and Approval Cost Analysis.” (Breakdown of out-of-pocket costs by phase: approx. $19M Phase 1, $71M Phase 2, $237M Phase 3, not including failures). N-SIDE Life Sciences (Derep, 2022). “What’s the average time to bring a drug to market in 2022?” (Citing PhRMA and BIO data: ~10–15 years on average; Phase I ~2.3 yrs, II ~3.6 yrs, III ~3.3 yrs, ~1.3 yrs for approval). Michael J. Fox Foundation (Brass, 2024). “What Does it Take to Get a Parkinson’s Drug Approved by the FDA?” (Overview of phases and FDA review steps; 10–15 years, $2.6B average; Phase I tests safety, Phase II efficacy, Phase III confirmatory; FDA NDA review 6–10 months). Mullard, Asher. “Parsing clinical success rates.” Nature Rev Drug Discov. 15, 447 (2016). (Summarizes BIO study; notes higher success in non-oncology, rare diseases up to ~25% success vs oncology ~5%). Glanz, Benjamin. “The Drug Development Process (RAI Explainer).” CSIS, Sept 6, 2022. (General overview; notes 1 in 5000 compounds makes it to market, 10–15 year timeline, ~$2.9B cost). Greenfield Chemical (Roden, 2023). “The Staggering Cost of Drug Development: A Look at the Numbers.” (Provides phase cost breakdown: Preclinical $15–100M; Phase I ~$25M; Phase II ~$60M; Phase III ~$350M avg, up to $1B; NDA filing ~$2M; Phase 4 $20–300M). U.S. FDA. “The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective.” (FDA Consumer info on development and approval process). European Medicines Agency. “Obtaining an EU marketing authorisation, step-by-step.” (EMA’s official outline of the centralised procedure; 210-day CHMP review, 67-day Commission decision). Schüller et al. “FDA and EMA expedited programs for anticancer drugs: analysis of review times.” Clin Pharmacol Ther. (2022). (Notes FDA has more expedited programs; median EU approvals ~136 days slower than US in

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