Development History of the Nucleotide Industry

Part I: A Tribute to the Pioneers

From the discovery of nucleotides as fundamental life substances, the elucidation of their molecular structures, the decoding of biosynthetic pathways, to the industrialization of fermentation processes and dual commercial applications in food flavor enhancement and nutritional fortification, nucleotides have undergone over 150 years of breakthroughs in basic scientific research and seven decades of iterative industrialization. Evolving from fundamental genetic building blocks of living organisms, nucleotides have branched into four core product categories: key flavor-enhancing ingredients for food, essential nutritional fortifiers for infant formula, biopharmaceutical intermediates, and immune nutritional additives for animal feed. This has fostered a full-chain industrial ecosystem spanning life sciences, the food industry, general health, livestock breeding, and biomedicine.

As pivotal functional monomers bridging fundamental life sciences and industrial raw materials for civilian use, the advancement of the nucleotide industry mirrors technological leaps across three generations of disciplines: modern biochemistry, molecular biology, and industrial fermentation engineering. It embodies the persistent dedication of life science researchers worldwide, fermentation engineering R&D teams, food ingredient research institutions, standard-setting organizations, and manufacturers across the entire industrial chain.

Hereby, we pay sincere tribute to all individuals, research teams, universities, research institutes and industrial enterprises that have dedicated themselves throughout the entire journey—from the discovery of basic nucleotide substances, molecular structure analysis, decoding of biological metabolic pathways, iteration of fermentative synthesis technologies, toxicological safety verification for edible use, research on nutritional functional mechanisms, global food compliance registration, formulation of domestic and international industrial standards, to full-scenario market commercialization. In accordance with principles of industrial competition protection and corporate privacy, specific enterprise names are omitted in this section. We extend special recognition to all domestic and international research institutions and manufacturers that have delivered groundbreaking contributions to the development of this industry.

Honor Roll of Contributors

(I) Core Scientists and Researchers (Chronological Order of Research Achievements)

1. ***Dr. Friedrich Miescher (University of Basel, Switzerland): Founding Father of Nucleic Acids and Nucleotide Research***

In 1869, his research team first isolated a phosphorus-rich acidic biomacromolecule from the nuclei of human white blood cells and named it "Nuclein". This discovery overturned the prevailing scientific consensus that proteins were the sole core functional substances within cells, proving for the first time that a novel fundamental life material resided in cell nuclei. It laid the original foundational framework for subsequent decomposition of nucleic acids and discovery of nucleotide monomers, kicking off over a century of research into nucleotides.

2. ***Professor Albrecht Kossel (University of Berlin, Germany, Nobel Laureate): Pioneer in Deciphering Nucleotide Molecular Structures***

During the 1880s to 1890s, he systematically dissected the chemical composition of nucleic acids and successfully isolated five nitrogenous bases: adenine, guanine, cytosine, thymine and uracil. He established that nucleic acids consist of three fundamental building blocks: bases, pentose sugars and phosphate groups. Further breakdown of nucleic acid macromolecules led to his formal definition of nucleotides as the minimal structural units of nucleic acids, clarifying structural distinctions between ribonucleotides and deoxyribonucleotides and constructing a complete theoretical framework for nucleotide chemistry. Awarded the 1910 Nobel Prize in Physiology or Medicine, his work provided core structural evidence for subsequent chemical synthesis and biotechnological fermentation production of nucleotides.

3. ***Dr. Phoebus Levene (Rockefeller Institute for Medical Research, USA): Elucidator of Nucleotide Glycosidic Bonds and Linkage Mechanisms***

Starting in 1909, he conducted comparative acidolysis and alkalolysis experiments to systematically study the structures of natural nucleotides such as inosinate. He identified the binding sites connecting ribose, nitrogenous bases and phosphate groups, proposing the classic molecular linkage model of nucleotides. He distinguished pentose sugar differences between ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), establishing the core mechanism by which linear polymerization of nucleotides forms long nucleic acid chains. His research filled critical theoretical gaps regarding the assembly of nucleotide monomers into macromolecules and refined the early biochemical theory of nucleic acids.

4. ***Academician Wang Debao (Shanghai Institute of Biochemistry, Chinese Academy of Sciences, China): Trailblazer of Chinese Nucleotide and Nucleic Acid Biochemistry, Founding Father of Domestic Flavor Nucleotide R&D***

From the 1950s to the 1980s, he established China’s first specialized nucleic acid research laboratory, filling the domestic void in fundamental nucleotide research. He spearheaded basic studies on isolation, purification and artificial chemical synthesis of nucleotide monomers, overcoming early technical bottlenecks in domestic raw

nucleotide purification. He also led preliminary national research layouts for flavor nucleotides, ending the complete absence of domestic fundamental nucleotide research. In 1981, as the principal academic lead, his team completed the world's first full artificial synthesis of biologically active yeast alanine transfer ribonucleic acid, propelling China to a global leading position in artificial synthesis of macromolecular nucleic acids. He built a comprehensive domestic theoretical system for chemical synthesis of nucleotides, laying a solid indigenous scientific foundation for later domestic industrialization of fermentative nucleotides and development of high-end medical-grade nucleotides.

5. ***Academician Wang You (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China): Core Leader of China's Artificial Nucleic Acid Synthesis***

From the 1960s to the 1980s, he collaborated closely with Academician Wang Debao on major national special projects for artificial synthesis of nucleotides and nucleic acids. He optimized key technologies for nucleotide fragment ligation and enzymatic synthesis, establishing microscale nucleotide preparation and activity detection systems adapted to domestic research conditions. His work resolved pre-industrial technical deficiencies in China's artificial nucleotide synthesis, refined foundational methodologies for nucleotide structural modification and purity quality control, and drove domestic fundamental nucleotide research from technology following overseas models to independent innovation. He facilitated standardized construction of China's early nucleotide research system.

6. ***The Oswald Avery Research Team (Rockefeller Institute, USA): Core Team Validating the Genetic Function of Nucleotides***

In 1944, their Streptococcus pneumoniae transformation experiment confirmed that nucleic acids (polymers of nucleotides) serve as biological genetic material. This established that nucleotides function not merely as cellular metabolic substrates but also as core carriers transmitting genetic information within living organisms. The discovery expanded the scope of nucleotide functional research, extending studies from food flavor applications to fundamental medical fields including genetic inheritance, cellular metabolism and immune regulation.

7. ***Professor Otowa Takeshi (The University of Tokyo, Japan): Discoverer of Nucleotide Umami Function and Industrial Pioneer of Flavor Nucleotides***

In 1950, he first isolated and purified 5'-guanylate (GMP) from dried shiitake mushrooms and verified its potent umami-enhancing properties. Subsequent team research validated the synergistic flavor effects of 5'-inosinate (IMP) and 5'-guanylate (GMP), discovering that blends of IMP and GMP deliver far stronger umami amplification than monosodium glutamate (MSG) alone. This breakthrough created an entirely new industrial segment for flavor nucleotides, supplying core functional theoretical support for global flavor enhancer industry upgrading and transitioning the condiment sector from the single MSG era to the compound flavor enhancer age.

8. ***Kyowa Hakko Fermentation Research Team (Japan): Originators of Industrial Fermentation Technology for Nucleotides***

During the 1950s and 1960s, the team overcame core technical bottlenecks in direct microbial fermentative production of nucleotides. They screened mutant strains with high

yields of inosinate and guanylate, resolved feedback inhibition mechanisms inherent to microbial metabolism, and developed the world's first full industrial process for direct fermentative nucleotide manufacturing. Replacing early nucleic acid enzymatic hydrolysis and chemical synthesis routes, this technology drastically cut production costs and elevated product purity, forming the foundational process framework for modern fermentative production of flavor nucleotides.

9. ***Domestic Expert Teams in Fermentation Engineering and Food Science (Jiangnan University, Tianjin University of Science and Technology, Hubei University of Technology, China National Research Institute of Food and Fermentation Industries): Core Force Behind Domestic Nucleotide Industry Localization and Technological Leadership***

Beginning in the 1980s, these institutions translated domestic fundamental nucleic acid research outcomes to address longstanding industrial pain points dominated by Japanese monopolies: proprietary high-yield strains, low fermentation conversion rates, poor extraction yields, insufficient product purity and exorbitant manufacturing costs. They conducted full-chain technical breakthroughs covering strain mutagenesis breeding, metabolic flux reprogramming, precise fermentation process control, downstream extraction and refining, and mother liquor resource recycling. Four landmark core technologies were sequentially developed: optimized enzymatic hydrolysis, improved direct fermentation, co-production of compound nucleotides, and high-purity monomer refining. These teams led the formulation of production workflows, testing protocols and national standards tailored to domestic fermentation infrastructure, enabling transformative growth of China's nucleotide industry from technology introduction and OEM processing to independent manufacturing, technological overtaking and global production capacity leadership.

(II) Core Research Institutions and University Teams

1. ***Institute of Physiological Chemistry, University of Basel (Switzerland): Birthplace of Nucleotide Research***

The institution completed the world's first isolation of Nuclein in 1869, launching systematic scientific study of biomacromolecules within cell nuclei and establishing foundational nucleic acid separation methodologies. It provided the original experimental paradigm for global fundamental nucleotide research and marks the starting point of all life science inquiry into nucleotides.

2. ***Institute of Physiological Chemistry, University of Berlin (Germany): Core Institution Establishing the Fundamental Theoretical System of Nucleotides***

It delivered landmark research on nucleic acid base separation, nucleotide monomer definition and nucleic acid polymerization mechanisms, establishing the foundational biochemical theory of nucleotides. This institute achieved the pivotal transition from material discovery to structural elucidation within the field, underpinning all subsequent global research on artificial synthesis, biological fermentation and functional applications of nucleotides.

3. ***Central Research Laboratories, Kyowa Hakko Fermentation (Japan): Global Cradle of Industrial Nucleotide Technology***

The institute pioneered screening of the first generation of fermentation strains, metabolic pathway modification and optimization of fermentation process parameters, launching the world's first full industrial nucleotide fermentation production line. It enabled the critical transformation of nucleotides from laboratory research samples to commercial food ingredients, maintaining long-term monopoly over global high-end nucleotide manufacturing technology and markets and guiding industrial process iteration across the first four decades of global nucleotide commercialization.

4. ***China National Research Institute of Food and Fermentation Industries: Domestic Incubator of Nucleotide Industrial Technology & Lead Standard-Setting Body***

China's earliest national-level platform dedicated to R&D breakthroughs in nucleotide fermentation technology. It completed China's first lab-scale and pilot-scale amplification trials for nucleotide production, resolved technical deficiencies of early enzymatic hydrolysis manufacturing processes, led formulation of China's first national food additive standards for nucleotides, and undertakes core national work on industrial safety evaluation, process optimization and regulatory filing, forming the bedrock of domestic nucleotide industrial development.

5. ***School of Biotechnology, Jiangnan University: Domestic Core Research Hub for Nucleotide Fermentation Process Upgrading and Strain Modification***

Focused on metabolic engineering modification of industrial microorganisms, the school targets critical industrial challenges including feedback inhibition during nucleotide fermentation, excessive by-product formation and low fermentation conversion efficiency. It developed innovative technologies including gene-edited high-yield strains, high-density fermentation and continuous fermentation, continuously boosting fermentation efficiency of domestic nucleotides, cutting unit energy consumption and advancing high-end, low-carbon transformation of the domestic industry.

6. ***Schools of Biotechnology, Tianjin University of Science and Technology & Hubei University of Technology: Core Technical Support Institutions for Downstream Nucleotide Refining and Compound Application Technologies***

Specializing in downstream processes including nucleotide separation and extraction, decolorization and impurity removal, crystallization purification and waste liquid resource recycling, these institutions refine manufacturing technologies for ultra-high-purity nucleotides. They simultaneously conduct research into nucleotide nutritional functions and blended formulations, supporting localized commercial adoption of nucleotides in infant formula, animal feed additives and functional food segments.

Part II: Research and Development History of Nucleotides

(I) Discovery of Life Substances and Embryonic Stage of Fundamental Theories (1860s–1940s)

- ***During the mid-to-late 19th century,***

  Modern biochemistry underwent rapid expansion as scientists focused on identifying core functional biomolecules within cells. Proteins were universally recognized as the sole primary active macromolecules, leaving nucleotides and nucleic acids largely unexplored in scientific research. The core objectives of this era were identifying the target substances, dissecting their chemical structures and defining their basic physicochemical properties.

- ***1869:***

  Swiss scientist Friedrich Miescher isolated a highly phosphorus-containing acidic organic compound from white blood cell nuclei, naming it Nuclein. This marked the first discovery of nucleic acid substances and the official launch of nucleotide research.

- ***1880–1900:***

  Research teams led by German scientist Albrecht Kossel systematically decomposed nucleic acid components, isolating five nitrogenous bases and confirming nucleic acids are composed of bases, pentose sugars and phosphate groups. He formally defined nucleotides as the minimal structural units of nucleic acids, distinguishing ribonucleotides and deoxyribonucleotides and establishing the foundational chemical theory of nucleotides.

- ***1900–1930:***

  Phoebus Levene's team analyzed internal chemical bonding within nucleotides and clarified the molecular mechanism by which nucleotide polymerization forms long nucleic acid chains, perfecting the basic molecular model of nucleotides. Concurrently, research teams worldwide extracted natural nucleotides from animal and plant tissues and microbial biomass, preliminarily identifying their core physiological roles in cellular energy metabolism and genetic material synthesis.

- ***1944:***

  The Avery team's Streptococcus pneumoniae transformation experiment confirmed nucleic acids (nucleotide polymers) as genetic material, revolutionizing core life science paradigms. Nucleotide research split into two distinct branches: fundamental research on genetic inheritance and cellular metabolism, and applied research focused on natural nucleotide extraction and functional development, defining dual developmental pathways for subsequent functional exploration and industrialization.

(II) Functional Exploration and Early Process Development Stage (1950s–1960s)

- ***The global food industry expanded rapidly throughout the 1950s,***

  Revealing critical limitations of single-ingredient MSG for umami flavor. The industry demanded novel flavor enhancers delivering stronger umami and synergistic taste amplification, driving the discovery of nucleotides' flavor functionality and initiating industrial applied research. Key breakthroughs of this period included validation of umami properties and development of the first three generations of laboratory-scale nucleotide manufacturing processes: nucleic acid enzymatic hydrolysis, chemical synthesis and microbial fermentation.

- ***1950:***

  Professor Otowa Takeshi's team at the University of Tokyo discovered the potent umami characteristics of 5'-guanylate (GMP) extracted from shiitake mushrooms. Follow-up experiments verified outstanding umami activity of 5'-inosinate (IMP) and demonstrated significant umami multiplication effects when combined with monosodium glutamate, formally unlocking the commercial value of nucleotides as innovative flavor enhancers.

- ***1955–1959:***

  Japanese research teams pioneered nucleic acid enzymatic hydrolysis technology, using yeast nucleic acid as raw material and nuclease hydrolysis to produce 5'-IMP and 5'-GMP for small-batch laboratory manufacturing. This constituted the world's first generation of nucleotide production processes, yet suffered severe drawbacks: high raw material costs, expensive enzyme preparations, difficult product separation and limited output, rendering it unfit for large-scale industrial manufacturing.

- ***1960:***

  Kyowa Hakko Fermentation delivered a landmark technological breakthrough. Ultraviolet mutagenesis generated high-inosinate-yield microbial strains, resolving endogenous metabolic feedback inhibition in microorganisms and creating the world's first industrial process for direct microbial fermentative nucleotide production. Eliminating reliance on nucleic acid feedstock and hydrolytic enzymes drastically reduced manufacturing costs, representing a milestone achievement in industrial nucleotide R&D.

- ***1960–1969:***

  Japan continuously optimized fermentation parameters and downstream extraction and refining workflows, gradually resolving challenges of high impurity levels in fermentation broth, low product purity and poor crystallization yields. Pilot-scale amplification of IMP monomers, GMP monomers and their blended product I+G was completed, bringing the global nucleotide industry to the threshold of full industrialization.

(III) Process Maturity and Overseas Monopoly Stage (1970s–1990s)

- ***From the 1970s to the 1990s,***

  Japan established a closed-loop full-industry chain for nucleotides, leveraging first-mover advantage to monopolize global access to proprietary strains, fermentation processes, refining technologies and market distribution channels. Parallelly, systematic edible safety toxicological verification of nucleotides was completed globally, triggering regulatory compliance filings across multiple nations. China launched preliminary technology tracking and targeted research, creating an industrial landscape defined by overseas technological monopoly and domestic import dependence.

- ***1970–1975:***

  Full-scale industrial fermentation production lines were fully deployed in Japan, enabling mass commercial production of 5'-IMP, 5'-GMP and blended I+G products. Nucleotides entered global markets as official food flavor additives, rapidly adopted in condiments, instant foods, meat products and savory snacks, driving comprehensive upgrading of the flavor enhancer sector.

- ***1975–1985:***

  JECFA, the U.S. FDA and the European Food Safety Authority sequentially completed acute, subchronic and chronic toxicological testing of nucleotides, confirming no cumulative toxicity, teratogenic or mutagenic hazards, or genotoxicity. Acceptable daily intake (ADI) thresholds for humans were established, completing food additive safety certifications across all major global economies and clearing regulatory barriers to full global market access.

- ***Post-1980:***

  China’s domestic food industry underwent rapid expansion with rising demand for high-end compound condiments. However, full Japanese monopoly over nucleotide manufacturing technology forced complete reliance on costly imported products, severely constraining development of downstream domestic food sectors. Domestic research institutes launched formal nucleotide technology research, initially replicating Japanese enzymatic hydrolysis workflows for lab-scale trials. Persistent barriers around proprietary strains and core process limitations prevented large-scale mass production for decades.

- ***1990–1999:***

  Domestic fermentation engineering teams delivered iterative technological upgrades, phasing out outdated enzymatic hydrolysis processes to advance direct microbial fermentation technology. Core bottlenecks including high-yield strain screening, fermentation process control and downstream separation purification were gradually overcome. In 1999, China achieved successful full industrial mass production of I+G, becoming the world’s third nation (after Japan and South Korea) to independently master complete fermentative nucleotide manufacturing technology and permanently dismantling long-term overseas technological monopolies.

(IV) Domestic Localization Breakthrough and Production Capacity Catch-Up Stage (2000s–2010s)

- ***The first decade of the 21st century***

Witnessed transformative growth of China's nucleotide industry: from zero domestic production to lab-scale manufacturing and full mass capacity expansion. Core development priorities centered on process optimization, cost reduction, quality improvement and national standard framework construction, enabling progressive import substitution in domestic markets while pioneering new product lines of nutritionally fortified nucleotides.

- ***2000–2005:***

  Multiple large-scale domestic nucleotide fermentation production lines were commissioned. Continuous optimization of fermentation media formulations, temperature and dissolved oxygen control steadily lifted fermentation conversion rates and extraction yields. Domestic nucleotides gradually replaced imported alternatives, capturing dominant share of China's condiment market.

- ***2006–2010:***

  Domestic research teams pioneered co-production technology for compound nucleotides, enabling simultaneous manufacturing of multiple nucleotide varieties within a single fermentation system to further cut production costs. In-depth research into nucleotide nutritional functions confirmed that exogenous nucleotide supplementation effectively supports infant intestinal development, enhances immune function and repairs intestinal mucosa. This expanded nucleotide applications beyond flavor enhancement to a brand-new segment of nutritional fortifiers for infant formula.

- ***2010:***

  China's first national food additive standard for nucleotides was released, unifying physicochemical indicators, testing methodologies and production hygiene specifications for disodium 5'-inosinate, disodium 5'-guanylate and disodium 5'-ribonucleotides (I+G). This resolved longstanding industry disorder caused by inconsistent product quality and lack of unified testing criteria, ushering the domestic nucleotide industry into an era of standardized development.

(V) Deepened Functional Development and Global Technological Leadership Stage (2010s–Present)

- ***From the 2010s to the present,***

  Global nucleotide research has shifted focus from basic production process optimization toward targeted functional development, high-value product innovation and green low-carbon process upgrading. China has delivered comprehensive technological overtaking via four core innovations: metabolic engineering strain breeding,

high-density fermentation, continuous manufacturing and mother liquor resource recycling. It now ranks as the world's largest nucleotide manufacturer and exporter, with nucleotide applications fully extended into emerging sectors including foods for special medical purposes, biomedicine, livestock immune nutrition and pet food.

- ***2010–2018:***

  Joint R&D initiatives between domestic universities and enterprises deployed gene-edited strain modification to directionally optimize microbial metabolic pathways, fully eliminating native cellular feedback inhibition. Nucleotide fermentation yields exceeded traditional industry ceilings, with product purity surpassing 99.5% and all key quality metrics outperforming Japanese and South Korean imported equivalents.

- ***2019–2022:***

  Green manufacturing technologies were fully rolled out across the industry, with widespread adoption of continuous fermentation, membrane separation refining and recycled fermentation mother liquor workflows. These innovations drastically reduced wastewater discharge and unit product energy consumption, resolving the longstanding pain points of high pollution and energy intensity characteristic of traditional fermentation industries and advancing green low-carbon transformation of the nucleotide sector.

- ***2023–2025:***

  Revised national food safety standards were sequentially issued, establishing differentiated quality specifications for three product categories: food flavor nucleotides, nutritional fortification nucleotides for infant formula and feed-grade nucleotides, alongside a tiered quality control framework. Concurrently, domestic breakthroughs were achieved in high-end biomedical-grade products including ultra-pure nucleotide monomers and modified nucleotides, breaking the final overseas technological monopoly in high-value pharmaceutical intermediates.

Part III: Commercialization Development History of Nucleotides

The commercial evolution of nucleotides aligns with simultaneous progress in global food regulation, iterative fermentation bioengineering technology, expansion of domestic manufacturing capacity, diversification of functional applications and restructuring of global supply chains. Over more than 150 years, the industry has traversed six distinct developmental phases: fundamental life science research, laboratory functional validation, overseas-monopolized industrialization, domestic import dependence, domestic substitution breakthrough, and China-led global dominance. A clear evolutionary trajectory emerges across this timeline: fundamental life substance → laboratory functional raw material → standardized food flavor ingredient → multi-scenario nutritional functional material → high-end biomedical monomer. A chronological breakdown by dimension is provided below:

(I) Functional Commercialization and Global Regulatory Approval (1950s–1990s)

- The 1950s through 1990s

  Constituted a critical era for formal validation of nucleotides' commercial value and global regulatory compliance. Landmark achievements included definitive confirmation of core umami functionality, completion of toxicological safety evaluations across dozens of nations, and acquisition of food additive market access credentials in all major global economies, laying robust regulatory foundations for mass industrial manufacturing and international trade.

- 1950:

  Scientific validation of nucleotides' umami multiplication effect formally established their commercial application potential, prompting global ingredient manufacturers to invest in nucleotide industrialization R&D.

- 1970–1980:

  JECFA completed comprehensive toxicological safety assessments of nucleotides, defined acceptable daily intake (ADI) limits and formally listed flavor nucleotides within the internationally recognized food additive catalog. The U.S. FDA approved IMP, GMP and I+G as legal flavor enhancers, while the EU assigned official food additive identification codes, completing regulatory clearance for core European and North American markets.

- 1980–1995:

  Japanese and South Korean nucleotide products entered Southeast Asia, China, Australia and other regional markets, forming an initial global nucleotide trade network. Parallel national safety assessments were completed across individual countries; by 1999, nucleotides secured food-use approval in over 60 nations and territories worldwide, emerging as one of the most widely recognized compound flavor ingredients globally and eliminating cross-border regulatory barriers to full international commercialization.

(II) Overseas Monopoly and Domestic Import Dependence (1980s–Late 1990s)

- From the 1980s through 1999,

  The global nucleotide industry operated under extreme oligopolistic control. Japanese corporations held exclusive ownership of all proprietary core strains, fermentation workflows and refining technologies, dictating global pricing power and controlling high-end markets. Lacking independent domestic manufacturing capacity, China relied entirely on costly imported products, leaving its downstream food industries vulnerable to external supply constraints.

- The 1980s

  Saw explosive growth in China's domestic condiment and instant food sectors. Single-ingredient MSG failed to meet demands for premium product formulation, making I+G an indispensable raw material for high-end food recipes. Sky-high import prices drastically inflated formulation upgrade costs for domestic food manufacturers, hindering high-end transformation of China's food industry.

- Mid-1980s to Mid-1990s:

  Multiple domestic research institutes attempted to replicate overseas production processes, yet persistent barriers including confidential proprietary strains, immature fermentation control technology and underdeveloped downstream extraction workflows yielded low product recovery rates, excessive impurities and manufacturing costs exceeding import prices. Large-scale domestic industrial production remained unachievable for over a decade, perpetuating full import reliance.

- 1999:

  Commissioning of China's first independently developed nucleotide fermentation production line enabled stable mass output of I+G, marking the definitive end of China's fully import-dependent era and dismantling the single-nation monopoly over the global nucleotide industry.

(III) Domestic Substitution and Establishment of National Standard Systems (2000s–2010s)

- 2000–2019

  Represented a pivotal phase of large-scale capacity expansion, full domestic import substitution and comprehensive national standard framework development for China's nucleotide industry. China evolved from zero production capacity to become the world's core manufacturing base, while establishing a complete national standard system covering food additive applications, nutritional fortification, production management and analytical testing methodologies.

- 2000–2008:

  Sustained release of domestic production capacity leveraged inherent advantages of local raw material and labor costs, delivering superior cost-performance for domestic nucleotides versus imported alternatives. Domestic products rapidly captured dominant share of China's condiment, snack food and meat processing markets, achieving complete import substitution across civilian food segments.

- 2010:

  GB 28302-2010 National Food Safety Standard – Food Additive Disodium 5'-Ribonucleotides was officially issued, filling the void of dedicated national standards

for nucleotides. It unified production, testing and quality control requirements industry-wide, resolving decades of unregulated fragmented standards.

- 2013–2019:

  The National Health Commission sequentially approved nucleotides as legal nutritional fortifiers for infant formula and foods for special medical purposes, defining permitted application ranges and maximum dosage limits. This unlocked high-value nutritional application markets for nucleotides, freeing the industry from exclusive reliance on low-margin flavor enhancer segments.

(IV) Diversified Application Expansion and Upgraded Functional Value (1990s–2020s)

Driven by mature manufacturing processes, perfected regulatory frameworks and deepened research into functional mechanisms, nucleotides have undergone three successive tiers of product positioning upgrades:

1. First-generation products: Simple umami amplifiers for MSG blending
2. Second-generation products: Nutritional fortifiers supporting human intestinal health and immune function
3. Third-generation products: High-end monomers for cellular metabolic regulation and biopharmaceutical synthesis

Application scope has continuously expanded across new industrial verticals.

- Early Industry Phase (1950–2000):

  Primary application focused solely on food flavor enhancement. Leveraging umami multiplication effects, nucleotides were blended with MSG for chicken bouillon, instant noodle seasonings and meat processing. Their core value lay in amplifying food umami, reducing MSG dosage and refining flavor profiles, with narrow, single-purpose application scenarios.

- Mid Industry Phase (2000–2015):

  Nutritional functionality achieved full commercialization. Extensive human clinical and animal trials confirmed exogenous nucleotides promote infant intestinal villus development, boost systemic immunity, accelerate post-surgical recovery and balance intestinal microflora. Nucleotides successfully penetrated infant formula, meal replacement and functional health supplement markets.

- Recent Industry Phase (2015–2025):

Industrial applications further expanded into livestock farming and biomedicine. Feed-grade nucleotides effectively boost stress resistance and immune capacity in livestock and aquaculture species while cutting antibiotic consumption in breeding operations. Modified nucleotides and ultra-high-purity nucleotide monomers serve as raw materials for mRNA vaccines and intermediates for nucleic acid therapeutics, entering high-value life science biomedicine verticals and driving exponential growth in overall industrial market value.

(V) Restructured Global Industrial Landscape and New Era of Comprehensive Chinese Leadership (2020–Present)

Backed by fully overtaken biofermentation technologies, large-scale green production capacity, a complete tiered standard system and robust multi-scenario application R&D capabilities, the global nucleotide industrial landscape has undergone thorough restructuring post-2020. China has supplanted Japan as the world's central leading entity in nucleotide research, manufacturing, export and standard formulation.

China's total nucleotide production capacity currently accounts for over 85% of global output, ranking the nation as the world's largest manufacturer, consumer and exporter of nucleotides. Domestic product portfolios span four core verticals: general food flavor enhancement, infant nutritional fortification, livestock immune nutrition and biomedicine, with bulk exports to more than 100 countries and territories worldwide. China holds dominant market share across all mid-tier civilian segments and mainstream high-end consumer markets globally.

The global industry now operates under a new differentiated competitive framework:

Japanese and South Korean enterprises focus on niche high-end biomedical verticals including modified nucleotides and custom ultra-pure monomers, retaining limited competitive advantages in specialized high-tech segments. Domestic Chinese manufacturers leverage fully integrated industrial supply chains, low-cost green manufacturing processes and continuously optimized strain modification technologies to fully capture civilian food, feed and health supplement markets, while advancing sustained R&D breakthroughs targeting high-end pharmaceutical raw material segments and gradually eroding overseas market share in premium verticals.

Looking forward, the nucleotide industry will continue advancing along four core development trajectories: green low-carbon fermentation, targeted metabolic strain breeding, high-value modified nucleotide production and nucleic acid drug raw material manufacturing. The industry's primary growth driver has shifted from historical capacity scale expansion to a high-quality development model centered on strain innovation, eco-friendly manufacturing, targeted functional design and domestic substitution of high-end specialty materials. China will maintain global leadership in iterative fermentation process development, industrial standard revision and emerging application exploration, driving the evolution of nucleotides from basic food ingredients to premium high-value life health raw materials.