

# Pharmadite™

## For Pharmaceutical Applications



The Pharmadite product line represents a new class of standard protected DNA phosphoramidites designed with highly controlled impurity profiles and exceptional overall purity. Pharmadite products fulfill all the requirements of starting materials for the manufacture of active pharmaceutical ingredients as defined in the EMEA 'Note for guidance on chemistry of the new active substance'\*<sup>1</sup>, making them suitable building blocks for oligonucleotide drugs.

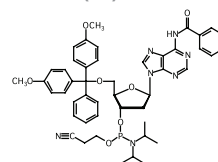
Pharmadite amidites are manufactured in scales of up to multi-hundred kilos, under certified ISO 9001 quality systems at SAFC's Proligo® Reagents manufacturing facility in Hamburg, Germany. We start with traceable synthetic raw materials, use highly controlled synthesis and purification processes, validated analytical methods and cleaning processes, all governed with strict change control and documentation to yield unprecedented high quality products with purity ratings at 99.5% or higher. All remaining impurities, if present, are identified and characterized at a level of 0.1%

The high level of control and documentation imposed at every step of the production process support regulatory requirements to make Pharmadite amidites ideal for pharmaceutical applications.

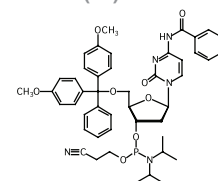
### Key Features

- Synthetic Starting Materials
- Consistent Quality
  - Raw Material Control and Traceability
  - Process Control
  - Tight Specifications
  - Validated Analytical Methods
- Known impurity profiles
- Available in large scale
- Reliable supply through our worldwide supply chain

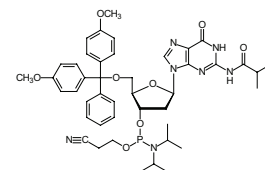
### DMT-dA(bz) Pharmadite



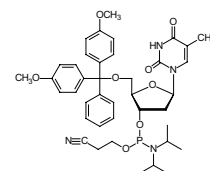
### DMT-dC(bz) Pharmadite



### DMT-dG(ib) Pharmadite



### DMT-dT Pharmadite



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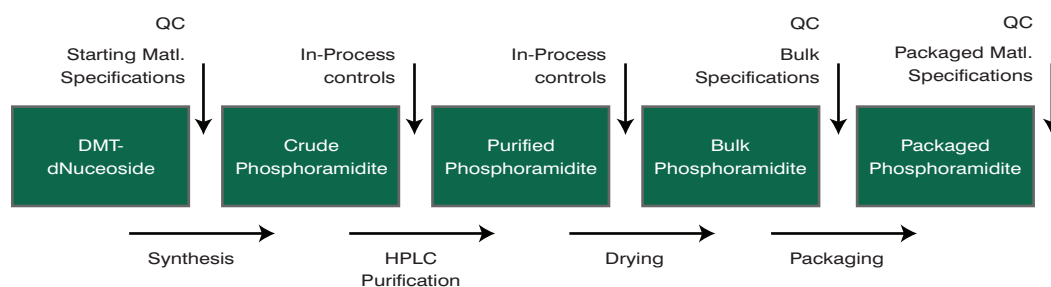
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## Manufacturing

Pharmadite amidites are prepared from DMT-protected nucleosides and the phosphitylating agent "bis-amide." The crude phosphoramidites are then purified by preparative HPLC, dried and packaged.

To ensure the highest quality our production process begins with starting materials that possess stringent specifications and defined impurity profiles. Our HPLC production line is cleaned using validated cleaning methods and cleaning verification is performed prior to each batch. Reactions are conducted at a minimum synthesis scale of 50 kg per batch. Each processing step is monitored using analytical in-process controls, including HPLC.



## Specifications

Pharmadite amidites are characterized by their exceptional purity and well-defined impurity profile. In particular, they are essentially free from contaminants which interfere in coupling reactions, such as other nucleosidic or non-nucleosidic phosphoramidites (P(III)-contaminants).

Characteristic	Acceptance Limit
Appearance	white to off white powder or granules
Appearance of Solution	≤ 10 Hazen (c = 0.2M in ACN)
Solubility	clear solution (c = 0.2M in ACN)
Identification	conforms
HPLC Purity	≥ 99.5 %area
Single Specified Impurity (see Table 2 for Reference)	≤ 0.3 %area
Single Unspecified Impurity	≤ 0.1 %area
<sup>31</sup> P NMR Purity	≥ 99.5 %area
<sup>31</sup> P NMR P(III) Impurities (@ 100 to 169 ppm)	≤ 0.1 %area
<sup>31</sup> P NMR P(V) Impurities (@ -25 to 99 ppm)	≤ 0.5 %area
<sup>31</sup> P NMR ≥170 ppm Impurities (@ 170 to 225 ppm)	not detected: S/N < 2.5
Residual Solvent Content	≤ 3.0 %wt
Water Content	≤ 0.40 %wt
Origin of Nucleoside	synthetic, (enzymatic)

Specified Impurities	A	C	G	T
DMT-dNucleoside-cyanoethyl-H-phosphonate	≤ 0.3%	≤ 0.3%	≤ 0.3%	≤ 0.3%
DMT-dNucleoside phosphoramidate	≤ 0.3%	≤ 0.3%	≤ 0.3%	≤ 0.3%
DMT-dNucleoside-diisopropylamino-H-phosphonate	not specified	not specified	≤ 0.3%	not specified
03'-Benzoyl-05'-DMT-dC(bz)	not applicable	≤ 0.3%	not applicable	not applicable



**SAFC** Supply Solutions™  
Inspiring Science

\*EMA: European Medicines Agency, <http://www.emea.eu.int>  
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