Sigma-Aldrich®
Lab & Production Materials

FAQ Sheet

ProClin™ Preservatives

Questions Addressing Regulatory Concerns

1) Can ProClin™ products be used for IVD manufacturing?

Yes,
ProClin™ products are dedicated for use in the Medical Devices (MD) and *in vitro* diagnostics (IVD) sector globally. The use of biocides to treat MD and IVD products is exempted from the Biocidal Products Regulation (BPR) as long as the MD/IVD products are in scope of the MD/IVD directives/regulations.

However,
Products not in scope for these MD/IVD definitions and related directives/regulations (e.g. veterinary related products, research use only (RUO) products, raw material), are in scope of the BPR with respect to preservation and other biocidal applications. This means ProClin™ products cannot be used for the manufacturing of these kinds of products in Europe. Additionally, there are some cases where the borders between the scope of the different legislations are not one hundred percent clear and an individual evaluation of the situation is needed.

The following table (see next page) should help decide whether the BPR is or is not applicable on different scenarios in your manufacturing process of MD or IVD products. Two principle activities are considered with respect to biocidal products (BP). First, the use of a BP by the MD/IVD manufacturer within the production of an MD/IVD. The second activity is the placing on the market of the MD/IVD product itself. Here the question to answer is if the MD/IVD product is regarded as a treated article (TA) in the sense of the BPR. One major aspect for the relevance is the location of the manufacturer, outside EU or inside EU.

Not all aspects might apply to the MD/IVD manufacturer itself: some aspects could also apply to its suppliers of raw materials or components. In each of the scenarios in the table, the applicability of the BPR is given as either yes or no. If the answer is “yes”, which means that the BPR is applicable, than the use of ProClin™ products is not permitted.

Definitions: MD, “Medical Device” in scope of Directives 90/385/EEC, 93/42/EEC or Regulation (EU) 2017/745; **IVD,** “In Vitro Diagnostic Medical Device” in scope of Directive 98/79/EC or Regulation (EU) 2017/746; **AS,** “Active Substance” as defined by BPR; **BP,** “Biocidal Product” as defined by BPR; **PT,** “Product-type” as defined by BPR; **TA,** “Treated Article” as defined by BPR; **RUO,** “Research Use Only” (Ref 12); **R&D,** “Research & Development” in the life cycle of an MD/IVD; **IUO,** “Investigational Use Only” in the life cycle of an MD/IVD; **Selective Agent,** A substance (a chemical agent, a dye or an antimicrobial agent) used to support/promote the growth of specific organisms (living cells), but inhibit the growth of another.

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	Activities by the Manufacturer	Use of a BP in production of an MD/IVD	Placing on the EU market as TAs
	Scenarios	**BPR applicable?**	**BPR applicable?**
Non-EU	**1) Non-EU production of MD/IVD, without AS or BP ending up in the MD/IVD** (import of finished MD/IVD into the EU)	**NO**	**NO**
Non-EU	**2) Non-EU production of MD/IVD intentionally containing biocidal AS** (e.g. preservative in an imported IVD)	**NO**	**NO**
Manufacturer located in EU	**3) Use of a substance for non-biocidal purposes** (e.g. alcohol as solvent or citric acid as a buffer)	**NO**	**NO**
Manufacturer located in EU	**4) Export to non-EU only**	**NO**	**NO**
Manufacturer located in EU	**5) Use of a chemical as a selective agent** (e.g. use of an antibiotic as a selective agent to produce antibodies)	**NO**	**NO**
Manufacturer located in EU	**6) EU production with AS/BP as raw material intentionally ending up in the MD/IVD** (e.g. adding a preservative to an IVD)	**NO**	**NO**
Manufacturer located in EU	**7) Commercialization/R&D/IUO of an MD/IVD** (e.g. clinical trials prior to final CE mark)	**TBD**	**NO**
Manufacturer located in EU	**8) EU production of MD/IVD, without AS or BP ending up in the MD/IVD** (e.g. disinfectant for machinery in production or for process and quality control)	**YES**	**NO**
Manufacturer located in EU	**9) Unintended residues of biocidal products in the finished product** (e.g. preservative of a raw material intentionally used upstream but without intended biocidal function in the finished product)	**YES**	**NO**

The major conclusions from the table above are:

1. The use of biocides and inclusion into MD/IVD sold outside the EU is **not within scope** of the EU BPR.
2. Incorporation of a biocide into an MD/IVD outside the EU followed by placing on the EU market and import into the EU is **exempt** from the BPR.
3. Manufacture of an MD/IVD containing a biocide in the EU for the purpose solely of exporting it is **exempt** and not in the scope of the BPR.
4. The manufacture of an MD/IVD containing a biocide in the EU for placement on the EU market when the AS or BP is included in its entirety in the MD/IVD is **exempt** from the BPR.
5. It remains unclear if the steps in R&D are or are not in the scope of the BPR. Further clarification from authorities are required.
6. The steps prior to CE-marking of the MD/IVD Investigational Use Only (IUO) are **most likely exempt** from the BPR.
7. In-process uses of biocidal products in manufacturing (without intentional incorporation of the active substance in the finished MD/IVD) are **mostly subject to** the BPR.
8. RUO products, veterinary MD/IVD products and raw materials themselves are **subject to** the BPR.

2) Is a ProClin™ product subject to REACH?

Yes,
ProClin™ products are subject to REACH as their intended uses are exempted from the BPR.

The active substances, CMIT/MIT (CAS 55965-84-9) or MIT (CAS 2682-20-4), as well as any other ingredient in the ProClin™ products (e.g. salts) need a registration if imported above 1 ton/annum. The net weight of each component needs to be used for the volume calculation.

3) Do I need an authorization from ECHA to use ProClin™ products?

No,
ProClin™ products do not fall under the BPR and are not regarded as biocidal products. They are therefore **not subject to the biocidal product authorization process.**

The ingredients of ProClin™ products are not regarded as substances of very high concern (SVHC) and **not subject to a REACH authorization process.**

4) What are the key differences between the various ProClin™ products?

ProClin™ Formulation Key Features

Features	ProClin™ 150	ProClin™ 200	ProClin™ 300	ProClin™ 950
Active ingredients (A.I.)	CMIT/MIT	CMIT/MIT	CMIT/MIT	**MIT**
% total A.I.	**1.5**	**1.5**	**3**	**9.5**
Stabilizer	**23-25% Mg salts**	**3% Mg & Cu salts**	**Alkylcarboxylate**	**none**
Matrix	Water	Water	**modified glycol**	Water
Working pH Range	2.5 - 8.5	2.5 - 8.5	2.5 - 8.5	**2 - 12**
Typical Dosage Levels	0.05 - 0.10%	0.05 - 0.10%	0.03 - 0.05%	0.05 - 0.10%
Shelf Life	2 years*	**1.5 years**	3 years	3 years
Temperature Range	<45 °C	<45 °C	<45 °C	**<90 °C**

Key formulation differences are highlighted

* Recent change from 3 years to accommodate high temperature regions that could impact shelf life.

CMIT, 5-chloro-2-methyl-4-isothiazolin-3-one; MIT, 2-methyl-4-isothiazloin-3-one

Characteristic	ProClin™ 150	ProClin™ 200	ProClin™ 300	ProClin™ 950
Compatible with Protein < 0.5%	●	●	●	●
Compatible with Protein > 0.5% < 2%	●	●	●	●
No / Low Salt (divalent)Requirement < 1.5mM	●	●	●	●
Enzyme Compatibility	●	●	●	●
Phosphate Buffer	●	●	●	●
HEPES Buffer compatibility	●	●	●	●
TES Buffer compatibility	●	●	●	●
TRIS Buffer compatibility	●	●	●	●
1° Amines (< 0.01%)	●	●	●	●
2° Amines (< 0.01%)	●	●	●	●
3° Amines (< 0.01%)	●	●	●	●
High pH Compatible > 8	●	●	●	●
High Temperature Stability > 45°C	●	●	●	●
Preservative shelf life > 2 yrs	●	●	●	●
High Concentration of Preservative (> 1.5%)	●	●	●	●
Control Bacteria and Fungi	●	●	●	●
Control Bacteria	●	●	●	●

● **= Yes** ● **= Variable** (confirm with testing) ● **= No**

5) Do the different ProClin™ products have different uses?

There could be situations of pH, temperature or addition of salts that affect which ProClin™ products may be selected.

ProClin™ 950 (MIT only) is less sensitive to pH and temperature.

The CMIT/MIT mixture typically has a more effective biocidal response on fungi.

6) Can I directly replace sodium azide or other biocides with ProClin™ preservatives, or do I need to perform efficacy testing etc.?

Any biocide or preservative used in the development and manufacture of a MD or IVD should be tested in the specific application and formulation.

While recommended dosages are suggested for ProClin™ products, there is no absolute concentration for all uses. Testing could include microbiological efficacy studies and stability studies for a particular formulation.

Each customer will need to establish their own criteria, as with any supplied raw material.

To Place an Order or Receive Technical Assistance

For more information:

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