Wroclaw, 15.09.2023

The order is implemented in connection with the preparation of applications for co-financing under the European Funds for Modern Economy Program (FENG), Priority: Support for entrepreneurs (FENG.01.01-IP.02-002/23), financed by the European Union and in accordance with the competition documentation this recruitment announced by the Polish Agency for Enterprise Development (PARP).

Number: **DOTO/103/2023/02**

Order title: **“Adsorbers with aptamers production service”.**

SECTION I: CONTRACTING PARTY

I.1. Name and address of the Ordering Party

DOTO MEDICAL sp. z o. o.
ul. Legnicka 48E
54-202 Wrocław
NIP 8943200107

I.2. CPV code for the order

CPV code: 73110000-6 Research services

SECTION II: SUBJECT OF THE ORDER

II.1. Mode of proceeding

This procedure is granted in the form of an inquiry, with the principle of competitiveness. The basis for initiating this procedure is the applicable Guidelines on the eligibility of expenditure for 2021-2027 of November 18, 2022.

II.2. Definition of the subject of the order

The subject of the order is a service consisting in the development and production of prototypes of a column filled with a resin with immobilized aptamers with affinity for selected molecular targets, acting as adsorbers capturing pathogenic molecules (e.g. proteins) in a device for assisted blood detoxification in the dialysis process in patients with chronic kidney disease for *in vivo* preclinical tests and clinical trials.

II.2.1. Name of the order:

"Adsorbers with aptamers production service".

Project Title: Development of breakthrough ABD technology for selective elimination of pro-inflammatory proteins from the blood of patients with chronic kidney disease**.**

II.2.2. Description and basic conditions of the subject of the order:

PACKAGE I: Production of adsorbers with aptamers for in vivo preclinical tests.

The subject of the order is a service consisting in the development (in cooperation with the Ordering Party) and production of prototype columns filled with a resin with immobilized aptamers with affinity for selected molecular targets, acting as adsorbers in a device for Adjunctive Blood Detoxification (ABD) in the dialysis process in patients with chronic kidney disease. The function of the adsorber will be to filter plasma separated from blood cells by the ABD device to selectively remove selected molecules (proteins, other molecular targets). Aptamers will constitute the active molecules of the adsorber. The order concerns project number PB103, which assumes the production of up to 50 final adsorbers with aptamers for *in vivo* preclinical tests. At this stage of the project, it is not possible to determine detailed technical parameters and the size of the

adsorber, which will be determined in earlier stages of the project, the aim of which is, among others, establishment of an adequate animal model for chronic kidney disease.

Order:

1. Design and implementation of prototype adsorbers adapted for *in vivo* preclinical testing with additional specifications (see requirements for product preparation), in accordance with the guidelines of the PN-EN ISO 13485 standard regarding prototyping of medical devices, including maintaining design documentation.
2. Iterative production of the adsorber prototype version based on correcting and improving previous versions in cooperation with the Ordering Party. It is planned to produce up to 10 variants of the adsorber prototype before its final form and technological parameters are determined.
3. Development of the production process of the final adsorber with a volume adapted to the animal model (up to 10 mL).
4. Production, sterilization and packaging of a series of up to 50 final adsorbers for pre-clinical testing with additional specifications (see product preparation requirements), in accordance with the guidelines of the PN-EN ISO 13485 standard for prototyping medical devices, including maintaining design documentation.
5. Product release parameters
   a. Sterility
   b. Endotoxin level: limit 0.5 EU/1 mL working volume of the adsorber
   c. Possible plasma flow rate through the adsorber is not less than 1 mL/min
6. A set of analytical tests (according to Table 1) to be performed at the product release time set as time zero (T0).

   Table 1. Analytical test suite for product release.

TEST TYPE		T0
Purity	Microbiological purity (sterility)	Yes
	Endotoxins level (LAL test)	Yes

7. Creation by the Bidder/Contractor of documentation for prototyping and production of adsorbers (participation in the creation of development documentation for a device whose active element is an adsorber with aptamers).
8. Deadlines
   a. Preparation of adsorbers with specific release parameters is planned for the period May 2024-May 2026.
   b. Preparation and delivery of adsorber prototypes - up to 3 weeks from the delivery of the resin with the conjugated aptamer by the Ordering Party.
   c. Preparation and delivery of the final batch of adsorbers - up to 4 weeks from the delivery of the resin with the conjugated aptamer by the Ordering Party.
   d. Providing documentation of the adsorbers' production within 2 weeks of delivery of the final batch of adsorbers.
9. Requirements for product preparation
   a. The resin with the immobilized aptamer, after being placed in the column, must be sterilized by a method that will not have a negative impact on the functionality of the adsorber and the safety of its use in the device (e.g. no leakage of the resin with the aptamer and/or the aptamer itself).

b. The sterilization method should be validated to obtain products with a sterility assurance level (SAL) of 10^6. The cycle should be compliant with the ISO 17665-1:2006 standard - Sterilization of products used in health care.
c. Adsorber elements must be non-pyrogenic and must not release substances/compounds that could have a harmful effect on the patient's body, such as: cytotoxic, genotoxic, allergenic, immunogenic, hemolytic effects.
d. The elements connecting the adsorber with the blood or plasma supply tubes should be compatible with the other elements of the device to ensure its consistency and sterile operation of the device.

10. The Ordering Party will provide the Bidder/Contractor with a sufficient amount of the resin with the conjugated aptamer for the column prototyping processes and for the final production of the developed adsorbers by the Bidder/Contractor.
11. The Ordering Party will provide documents on prototyping of the adsorber manufactured for in vitro tests, necessary for work on developing a prototype of the adsorber for in vivo tests.
12. The Ordering Party will not disclose the full sequence of the aptamer.
13. Intellectual property rights created or obtained as a result of research conducted by the Bidder belong to the Ordering Party.

PACKAGE II: Production of adsorbers with aptamers for clinical trials (FTIH).

The subject of the order is a service consisting in the development (in cooperation with the Ordering Party) and production of prototype columns filled with a resin of immobilized aptamers with affinity for selected molecular targets, acting as an adsorber in a device for Adjunctive Blood Detoxification (ABD) in the dialysis process in patients with chronic kidney disease. The function of the adsorber will be to filter plasma separated from blood cells by the ABD device to selectively remove selected molecules (proteins, other molecular targets). Aptamers will constitute the active molecules of the adsorber. The order concerns project number PB103, which assumes the production of 25 final adsorbers with aptamers for FTIH clinical trials. At this stage of the project, it is not possible to determine the technical parameters and size of the adsorber.

Order:

1. Design and construction of a prototype adsorber adapted to a clinical trial with additional specifications (see: requirements for product preparation), in accordance with the guidelines of the PN-EN ISO 13485 standard regarding prototyping of medical devices, including maintaining design documentation.
2. Iterative production of the adsorber prototype version based on correcting and improving previous versions in cooperation with the Ordering Party. It is planned to produce up to 10 variants of the adsorber prototype before its final form and technological parameters are determined.
3. Development of the production process of an adsorber prototype with a volume of up to 50 mL. At this stage of the project, it is not possible to determine the exact volume of the adsorber.
4. Production of a batch of 5 final adsorbers in accordance with the guidelines of the PN-EN ISO 13485 standard regarding prototyping of medical devices and GLP/GMP standards, including maintaining design documentation for tests (including biocompatibility).

5. Production, sterilization and packaging of a series of up to 20 adsorbers for a clinical trial in accordance with the guidelines of the PN-EN ISO 13485 standard regarding prototyping of medical devices and GLP/GMP standards, including maintaining design documentation for tests.
6. Release parameters
a. Sterility
b. Endotoxin level: limit 0.5 EU/1 mL working volume of the adsorber
c. Possible plasma flow rate not less than 10 mL/min
7. A set of analytical tests (according to Table 2) to be performed at the product release time set as time zero (T0).

Table 2. Analytical test suite for product release.

TEST TYPE		T0
Purity	Microbiological purity (sterility)	Yes
	Endotoxins level (LAL test)	Yes

8. Creation of documentation for prototyping and production of adsorbers (participation in the creation of development documentation for the ABD device).
9. Deadlines
   a. Preparation of adsorbers with specific release parameters is planned for the period April 2025 - May 2026.
   b. Preparation and delivery of adsorber prototypes - up to 3 weeks from the delivery of the resin with the conjugated aptamer by the Ordering Party.
   c. Preparation and delivery of a batch of 5 adsorbers for testing (including biocompatibility) - up to 4 weeks from the delivery of the resin with the conjugated aptamer by the Ordering Party.
   d. Preparation and delivery of the final batch of 20 adsorbers for clinical trials - up to 4 weeks from the delivery of the resin with the conjugated aptamer by the Ordering Party.
   e. Providing documentation of the adsorbers' production within 2 weeks of delivery of the final batch of adsorbers.
10. Product preparation requirements
   a. After packing into the column, the resin with the immobilized aptamer must be sterilized using a method that will not have a negative impact on the functionality of the adsorber and the safety of its use in the device (e.g. no leakage of the resin with the aptamer and/or the aptamer itself).
   b. The sterilization method should be validated to obtain products with a sterility assurance level (SAL) of 10^6. The cycle should be compliant with the ISO 17665-1:2006 standard - Sterilization of products used in health care.
   c. Adsorber elements must be non-pyrogenic and must not release substances/compounds that could have a harmful effect on the patient's body, such as: cytotoxic, genotoxic, allergenic, immunogenic, hemolytic effects.
   d. The elements connecting the adsorber with the blood or plasma supply tubes should be compatible with the other elements of the device to ensure its consistency and sterile operation of the device.
11. The Ordering Party will provide the Bidder/Contractor with a sufficient amount of the resin with the conjugated aptamer for the column prototyping processes and for the final production of the developed adsorbers by the BidderContractor.
12. The Ordering Party will provide documents from the prototyping of the adsorber manufactured for in vivo preclinical tests.

13. The Ordering Party will not disclose the full sequence of the aptamer.
14. Intellectual property rights created or obtained as a result of research conducted by the Bidder belong to the Ordering Party.

II.2.3. Offer factors:

1. The possibility of submitting a partial bid is not admissible/ is admissible. When dividing the procedure into Package, each will be assessed separately.
2. The possibility of submitting a variant bid is not admissible.
3. The binding period with the bid: 60 days from the date specified in II.4.4. p.1.

II.3. Requirements for the Bidders:

1. The Ordering Party reserves that offers may only be submitted by Bidders who:
   a. are authorized to perform specific activities or activities, if the right imposes an obligation to have them to perform the activity covered by the contract,
   b. have a representative with biotechnology or related education (e.g. biology, biophysics, bioengineering) to contact the Ordering Party, consult and coordinate orders,
   c. have the necessary knowledge and experience in designing biomedical equipment,
   d. preference will be given to subcontractors who have documented experience with apheresis, dialysis devices or other medical devices containing pumps and filters and a documented history of similar orders performed in the last 4 years,
   e. it is advisable that the Bidder's resources include experienced production engineers with experience in designing medical devices and adapting the production line to this type of orders.
2. From the procedure are excluded Bidders who are personally or financially related to the Ordering Party. Financial or personal relations are understood as the relationship between the Bidder and the Ordering Party, or the persons authorized to incur liabilities on behalf of the Ordering Party or persons performing on behalf of the Ordering Party activities related to the preparation and conduction of this procedure, consisting particularly of:
   a. participating in the company as a partner in a civil law partnership or partnership.
   b. holding at least 10% of shares.
   c. acting as a member of the supervisory or management body, proxy, attorney.
   d. marriage, kinship, or affinity in a straight-line, second-degree affinity or second-degree affinity in a sideline or adoption, care, or guardianship,
   e. being in such a legal or factual relationship with the contractor that there is a reasonable doubt as to impartiality or independence.
3. The Ordering Party will consider the above conditions to be met if the Bidder submits together with the offer statement on meeting the above-mentioned conditions for participation in the proceedings. Evaluation of the fulfillment of the above-mentioned conditions will be made based on fulfillment / non-fulfillment.
   Bidders that do not meet the conditions descriresin in Section II.3 will be excluded from the proceeding.

II.4. Submission of the tenders:

II.4.1. Basic requirements

1. Each Bidder may submit only one offer.
2. The offer must be prepared strictly in accordance with the requirements set out in this specification.
3. The offer must be signed by the person(s) authorized to represent the Bidder.
4. The authorization of the persons signing the offer to sign it must result directly from the documents attached to the offer.
5. The documents attached to the offer should be completed and signed by the Tenderer.
6. The cost of preparing and delivering the offer is covered by the Bidder.

II.4.2. Form of the tender

1. The offer must be made in Polish or English and be in writing.
2. The entire offer should be submitted in a form that prevents its accidental incompleteness.
3. It is advisable to number all written pages of the offer and it is required to initial them by the person (or persons, if two or more persons are authorized to represent the Bidder) signing the offer in accordance with the content of the document specifying the legal status of the Bidder or the content of the power of attorney attached to the offer.
4. Documents may be presented in the form of originals or copies certified by the Bidder as true copies. Statements drawn up on the basis of the templates attached to this specification must be submitted in the original form.
5. Electronically signed documents are accepted.

II.4.3. Offer content.

1. The offer must be submitted by an authorized person/person.
2. The offer should contain attachments signed by authorized persons, at least:
   a. document authorizing/authorization for the person submitting the offer,
   b. Attachment No. 1 - completed offer form along with statements regarding the Bidder,
   c. Attachment No. 2 - statement on the lack of links between cooperating entities.
3. It is acceptable to sign and submit an offer in electronic form.

II.4.4. Place, date and manner of submitting the offer.

1. The offer must be submitted by 16.10.2023 CET inclusive,
2. The offer should be submitted directly to the European Funds Competitiveness Database as an offer for the procedure in question (https://bazakonkurencyjnosci.funduszeeuropejskie.gov.pl/).
3. Offers received after the deadline will be returned to the Bidders without their evaluation as invalid.

II.5. Mode of evaluating the tenders

1. The Ordering Party's will examine whether the tenders meet the formal conditions. Offers that do not meet the formal conditions will be rejected and will not be evaluated.
2. The Ordering Party's Committee evaluates offers that have not been rejected for formal reasons. The offers will be analyzed by the Ordering Party within 2 working days from the date of the deadline for submission of offers, with the proviso that if the Bidders are requested to provide additional explanations

or supplements, the deadline for evaluating the offers shall be extended by the time limit indicated for the Bidder's response specified in point II. 5.3.

3. In order to provide answers related to the clarification of the offer, 2 working days are assumed from the date of delivery of the inquiry/request for clarification by the Ordering Party.
4. After analyzing the offers and considering - in accordance with the principle of competitiveness - the submitted offers, the Ordering Party will publish the results in the Competitiveness Center of European Funds (https://bazakonkurencyjnosci.funduszeeuropejskie.gov.pl/).

II.6. Rejection of the offer, exclusion of the Bidder

1. The Ordering Party rejects the offer if:
   a) its content does not correspond to the content of this inquiry or is incomplete,
   b) its submission constitutes an act of unfair competition within the meaning of the provisions on unfair competition,
   c) did not submit to the Ordering Party explanations concerning the content of the submitted tender, if requested,
   d) was submitted by a Bidder who does not meet the criteria of this procedure or by an excluded Bidder,
   e) is invalid on the basis of separate regulations.

1. Bidders are excluded from the procedure, if:
   a) directly performed activities related to the preparation of the procedure or used persons participating in these activities to prepare the tender, unless the participation of these contractors in the procedure does not impede fair competition,
   b) they did not agree to extend the period of validity of the offer,
   c) submitted false information affecting or likely to affect the outcome of the proceedings,
   d) did not meet the conditions for participation in the procedure,
   e) are personally or financially related to the Ordering Party.
2. The tender of excluded Bidder is considered to be rejected.

II.7. Criteria for tenders evaluation

1. Formal assessment - will be made on the basis of attachments, documents and statements on meeting the conditions for participation in the procedure specified in point II.3. Offers that do not meet at least one of the conditions descriresin in point II.3. will be rejected.
2. The Ordering Party will evaluate offers that are not subject to rejection, submitted by Tenderers who are not subject to exclusion from the proceedings, according to the following criterion:

Criterion - Price - weight 100

The number of points for the price criterion will be calculated taking into account valid (not rejected) offers submitted by Bidders not excluded from the procedure according to the following formula (counting to two decimal places):

Number of points = (C_{min} / C_{bids}) * 100 points

Where:

C_{min} - the lowest price (NETT) from all submitted offers

$C_{of\ the\ offer}$ - the price (NETT) of the examined offer

The maximum deadlines for the performance of the entire service are specified in point II.2.2 and III.3.

3. To evaluate the price criterion, the net prices of the of individual Package will be considered. The net offer price in Polish zloty (PLN) will be assessed. In the case of bids submitted in a currency other than PLN, the average exchange rate of the National Bank of Poland on the date of bid submission will be used for currency conversion, with a precision of 4 decimal places.
4. The most advantageous offer will be the offer that meets the conditions specified in point. II.2.3, II.3, II.4 which will receive the highest number of points determined with an accuracy of 2 decimal places.

II.8. Terms of settlement

1. The Ordering Party anticipates settlements based on an invoice, payment method - bank transfer.
2. Payment deadline: 30 days from delivery of a correctly issued invoice. The Ordering Party allows the invoice to be delivered electronically to the address indicated in the contract.
3. The Ordering Party allows the possibility of making an advance payment.

SECTION III: ADDITIONAL INFORMATION

III.1. Project financing:

The Ordering Party informs that it intends to implement the project with the use of European Union Funds, the European Funds for Modern Economy Program (FENG), Priority: Support for entrepreneurs.

III.2. Forms of communication

1. The ordering party is not obliged to conduct the procedure in accordance with the Public Procurement Act.
2. The content of the inquiry is available at the headquarters of the Ordering Party's Project Office: ul. Legnicka 48 E, Wrocław, as well as in the European Funds Competitiveness Database https://bazakonkurencyjnosci.funduszeeuropejskie.gov.pl/.
3. Questions specifically related to the request for quotation should be submitted directly via **the Competitiveness Database** ("Questions" tab). **and additionally** to the e-mail address: info@dotomedical.com.
4. The Ordering Party will respond to questions by e-mail within 2 business days of receiving the inquiry, provided that the questions are received no later than 3 business days before the date of submission of offers.
5. If the question concerns confidential information resulting from the specificity of the subject of this Inquiry, the answer to such question will be provided individually after signing the Confidentiality Obligation by the Party submitting such a question. In this case, the Ordering Party will respond within 2 business days of receiving a signed copy of the Confidentiality Obligation.
6. If answers to questions or reported problems involve changes to the terms of the order, all Bidders will be notified of the changes by e-mail or phone, and moreover, questions and answers as well as changes to the terms and conditions of the contract will be made available in the European Funds Competitiveness Base and available at the Ordering Party's Project Office. In such a situation, the Ordering Party may extend the deadline for submitting offers.

III.3. Term of contract execution

The deadlines for carrying out individual tests are specified below:

- Package I: May 1, 2024 – May 30, 2026;
- Package II: April 1, 2025 – May 30, 2026.

Dates may be changed by mutual consent.

III.4. Important to both parties' provisions of the agreement

1. After the completion and publication of the results of this tender procedure, the Ordering Party and the selected Bidder will sign a relevant Conditional Cooperation Agreement. The implementation of this agreement will be conditional on granting funding in the competition 1.1 SMART Path, European Funds for a Modern Economy (FENG**.01.01-IP.02-002/23).** The contract will be prepared jointly by the Employer and the selected Bidder based on the provisions contained in this request for proposals.
2. After the Awarding Entity receives the co-financing, i.e. after signing and entering into force of the co-financing agreement with the appropriate Intermediate Body for the competition, the Awarding Entity and the Contractor will sign the final agreement.
3. The Agreement may be terminated at any time with the consent of both Parties.
4. The Ordering party may withdraw from the contract in the event of a significant change in circumstances that could not have been foreseen at the time of concluding the contract.
5. Termination and withdrawal from the contract must be made in writing to be effective, otherwise they will be null and void.
6. The contract expires after the time for which it was concluded or when circumstances occur for which the parties are not responsible, and which prevent its further performance.
7. The conditional agreement will expire if funding is not granted to the Ordering Party.
8. The Ordering Party permits the amendment of the contract in the form of an annex in case of:

a. if there is a necessity for the Intermediary Body to change the manner of performance of the contract by the Contractor,
b. when the deadlines for completing the stages of the project under which the contract is implemented change,
c. material changes in the subject matter and manner of performance of the Agreement not caused by the act or omission of any of the Parties of the Agreement,
d. force majeure, which prevents the subject of the Agreement to be performed in accordance with the specifications of the order, including the deadlines indicated in point III.3.

Attachment No. 1 - Offer form.

Offer form (TEMPLATE)

…….. ……..

…….. *(place and date)*

……..

……..

(name and address of the Bidder)

Offer in the procurement procedure conducted in the form of a request for proposals, maintaining the principle of competitiveness, in accordance with the Guidelines on the eligibility of expenditure for 2021-2027 of November 18, 2022.

Number: **DOTO/103/2023/02**

Order Name: **"Adsorbers with aptamers production service".**

1. **WE SUBMIT** The Tender for the performance of the subject of the contract and we declare that we will make them under the conditions specified in the request for proposal No DOTO/103/2023/02 with attachments.

2. **WE OFFER:** net unit prices (PLN/EURO/USD) * and net final prices (PLN/EURO/USD) * - after multiplying net unit prices by the planned quantity for each item in accordance with the table below:

No	Order description	Unit	Offered unit net price (....)*	Number of planned units to order (maximum)	Offered final max. net price (...) * [4x5]
1	2	3	4	5	6
1	Production of up to 50 adsorbers with aptamers for in vivo preclinical studies	Item		50	
2	Production of up to 25 adsorbers with aptamers for clinical trials (FTIH)	Item		25	

*- *the correct currency of the offer*

SUM

NET .... [.... .]*
(in words: .... [.....])*.
GROSS .... [.... .]*
(in words: .... [.....])*.

**- enter the correct total value and currency of the offer*

The above price includes all costs related to the execution of the order, in accordance with the requirements specified in the Inquiry No. DOTO/103/2023/02.

3. WE DECLARE that:

a. we will perform the subject of the order in accordance with the provisions of procedure No DOTO/103/2023/02,
b. we have read the content of the request for quotation DOTO/103/2023/02and all its provisions are fully understandable and acceptable to us,
c. we accept all deadlines included in the request for quotation no. DOTO/103/2023/02,
d. we are authorized to perform specific activities or activities, if the right imposes an obligation to have them to perform the activity covered by the contract,
e. we have a representative with biotechnology or related education (e.g. biology, biophysics, bioengineering) to contact the Ordering Party, consult and coordinate orders,
f. we have the necessary knowledge and experience in designing biomedical equipment,
g. we have documented experience with apheresis, dialysis devices or other medical devices containing pumps and filters and a documented history of similar orders performed in the last 4 years,

h. we have experienced production engineers with experience in designing medical devices and adapting the production line to this type of orders,
i. this offer is public.

Forewarned of liability for making a false statement or concealing the truth, we hereby declare that the above-mentioned the data is true.

4. WE ARE CONSIDERED bound by this offer for a period of 60 days from the deadline for submitting offers.

5. ALL CORRESPONDENCE regarding these proceedings should be addressed to:

First name and last name …….

Address: …….

Telephone: …….

E-mail adress: …….

6. This OFFER is submitted on _____ consecutively numbered pages and is accompanied by the following declarations and documents:

1)..... .....
2)……
3)……

_____ _____

(place, date)

Attachment No. 2

……. …….

……. *(place and date)*

…….

……..

(name and address of the Bidder)

Statement on the lack of links between cooperating entities

I declare that the Bidder submitting the offer is not related personally or by capital to the Ordering Party.

Capital or personal connections are understood as mutual connections between the Bidder and the Ordering Party or persons authorized to enter into obligations on behalf of the Ordering Party or persons performing on behalf of the Ordering Party activities related to the preparation and conduct of the procurement contractor selection procedure in the procedure no. DOTO/103/2023/02 entitled: "Adsorbers with aptamers production service ", consisting in particular of:

a) participating in a company as a partner in a civil partnership or partnership;
b) owning at least 10% of shares or shares;
c) acting as a member of the supervisory or management body, proxy, proxy;
d) being married, in a relationship of consanguinity or affinity in the direct line, in a second-degree relationship or in a second-degree affinity relationship in the collateral line, or in a relationship of adoption, care or guardianship,
e) being in such a legal or factual relationship with the contractor that there is a reasonable doubt as to impartiality or independence.

There are no above-mentioned connections between the Ordering Party and the Bidder.

_____, on __ __ 2023

(date and signature of the Bidder)