Consensus Recommendations for

Pleuropulmonary blastoma
in children and adolescents

Version 13

The ExPO-r-Net Project
ExPO-r-Net is a 3-year project aiming at building a European Reference Network (ERN) for Paediatric Oncology and reducing the current inequalities in childhood cancer survival and healthcare capabilities in different EU Member States.

Co-funded by the Health Programme of the European Union
Summary:
Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical of pediatric age, while other more commonly arise during adulthood and only rarely develop in children. Using the definition any solid malignancy or borderline tumor characterised by an annual incidence < 2/million children <18 years old and/or not already considered in other clinical trials the European Cooperative Study group for Pediatric Rare Tumors (EXPeRT) has identified a number of pediatric VRT (1). Due to the low number of patients it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it hard to arrive to evidence-based treatment guidelines. As a consequence, the treatment of patient with VRT is often individualized. Pleuropulmonary Blastoma (PPB) is a rare tumor typical of young children. Its exact incidence is difficult to establish. Data from registries propose an incidence from 0.18 to 1.9 per million children < 15 years (SEER unpublished results, 2). However prospective registration of patients on a national Registry found a higher number of cases (2) suggesting that PPB may not be well represented in general population based registries probably because its difficult categorization. Despite its rarity a number of effort has been made in the last decades to clarify its biology and identify effective treatment, but standard guidelines are not available

Objective: To establish internationally recognized recommendations for the diagnosis and treatment of children and adolescents with PPB. This constitute one of the deliverables of EXPORNET, an EU funded project.
Methodology
According to Cochrane methodology the grade of evidence can be classified from Grade I to III.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>RCT or RCT review</td>
</tr>
<tr>
<td>IA</td>
<td>Calculation of sample size and accurate, standard definition of outcome variables</td>
</tr>
<tr>
<td>IB</td>
<td>Accurate and standard definition of outcome variables</td>
</tr>
<tr>
<td>IC</td>
<td>Neither of the above</td>
</tr>
<tr>
<td>II</td>
<td>Prospective study with a comparison group (non-randomized controlled trial, good observational study) or retrospective study with controls effectively for confounding variables</td>
</tr>
<tr>
<td>IIA</td>
<td>Calculation of sample size and accurate, standard definition of outcome variables and adjustment for the effects of important confounding variables</td>
</tr>
<tr>
<td>IIIB</td>
<td>One or more of the above</td>
</tr>
<tr>
<td>III</td>
<td>Retrospective or observational or cross-sectional studies</td>
</tr>
</tbody>
</table>

EXPeRT recognized that due to the rarity of this tumor, no evidence of grade I or II exists. Therefore, recommendations for VRTs must be developed based on the evidence collected from published series, case reports (grade III) and personal expertise.

To identify shared recommendations, EXPeRT designed the following procedure:
- Identification of the tumor of interest on the base of its relevance, and previous EXPeRT experience, (i.e. data analysis and publication)
- Designation of two coordinators for each VRT on the basis of their experience (data analysis, publications, personal experience).

Coordinators have to
- Search the medical literature and select the relevant papers
- Propose a series of recommendation in a form of a first draft of recommendations
- Identify the main diagnostic and therapeutic problems for the designated VRT. The first draft is circulated, along with the relevant publications, to all member of EXPeRT.

A second draft of recommendations is produced taking into account proposals from EXPeRT. The second draft is proposed to external experts identified by the coordinators on the basis of a recognized experience. A third draft is then produced and circulated to a larger group of people with experience on PPB (2 to 4 people for each EXPERT Countries identified by the national coordinators). A fourth draft is created, circulated in a form of questionnaire to the whole group and finally discussed at a consensus conference. Each group member had to vote the different recommendations.
The “strength” of recommendations is categorized as follow:
- Highly recommended (HR) hi: 95% of experts agree
- Recommended (R): at least 80% of experts agree
- Possible (P): 60 to 80% of experts agree
- Agreement not possible (ANP): less than 60%

The final document including recommendations will be available in EXPORNET and EXPeRT website (www.raretumors-children.eu) and periodically updated.

**Warning:** These guidelines may change over time according to new data. The local clinician remains responsible for the care of his patient. The EXPeRT members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with members of these groups via the expert website:  **www.raretumors-children.eu**
Background

Pleuropulmonary blastoma (PPB) is a very rare and highly aggressive neoplasm arising in the lungs and presenting in early childhood, with most cases diagnosed in children less than 6 years of age. It is a dysembryonic malignancy believed to arise from the pleuropulmonary mesenchyme. PPB is classified into 3 interrelated clinico-pathologic entities on a developmental continuum. PPB is classified by the macroscopic appearance as type I (cystic), type II (solid and cystic), and type III (solid). The solid component of both type II and III has mixed-pattern including high grade sarcoma elements (3-5). Type I cystic PPB may progress to the aggressive Type II and Type III PPB but can often regress by losing malignant elements to the Type Ir (6).

PPB is distinguished from adult-type pulmonary blastoma by the absence of malignant epithelial components. Microscopically, PPB is characterized by blastematose islands with high mitotic activity associated with areas of spindle cells that can be undifferentiated or in various stages of malignant differentiation (rhabdomyosarcoma, chondrosarcoma, liposarcoma).

This tumor is the seminal disease of the spectrum of the DICER1 mutation related tumors which includes sex cord stromal ovarian tumors, thyroid nodular disease and carcinoma, cystic nephroma, pineoblastoma, pituitary blastoma, cervical rhabdomyosarcoma, ciliary-body medulloepithelioma and nasomesenchymal hamartoma (7-9).

Multimodality treatment has increased the possibility of survival, and approximately> 90% of children with Type I, > 70% Type II and > 50% Type III can be cured). Surgery is important to resect the lesion at diagnosis or after a neo-adjuvant treatment that include chemotherapy, with sometime adjuvant radiotherapy (6,10).

No prospective or comparative studies have been published in PPB so far. All recommendations presented here are therefore based on a grade III level of evidence.
Recommendations

INITIAL TUMOR ASSESSMENT:

PPB should be suspected when a young child presents with a pulmonary lesion that can be completely cystic, cystic with a solid component or completely solid.

A PPB diagnosis could be challenging in case of pure cystic lesions that need to be differentiated from other congenital cystic pulmonary lesions. Similarly, a solid lesion needs to be distinguished from other paediatric tumors.

PPB in children is characterized by symptoms often mistaken for respiratory infection, pneumothorax or lung malformation. The tumor is usually located in the lung, but it may extend to the mediastinum, diaphragm and/or parietal pleura. Type I PPB is a localized tumor but metastasis are present at diagnosis in less than 10% of types II-III PPB, most frequently located in the brain, bones and liver.

When a type II-III PPB is suspected, a histological diagnosis through a surgical procedure or fine needle biopsy must be obtained (see surgery section).

Staging investigations:

The primary tumor and its loco-regional tumor extension must be evaluated by Chest Computed Tomography (CT) with contrast enhancement. An evaluation of lymph nodes, mediastinum, cardiac and pericardial involvement must be done. This investigation should be extended to the abdomen to investigate diaphragm and liver involvement [HR]. Thoracic MRI could be considered [R].

Distant metastasis investigation should be searched in case of type II-III PPB include

- Brain MRI.
- Radionuclide Bone scan
- Echocardiography to identify vascular invasion and intra-cardiac involvement.

There are no data about the use of PET for evaluation of primary tumor and metastatic dissemination. As in other solid tumors, in older patients, PET may be of interest to evaluate response to therapy and can probably substitute bone scan.

Additional evaluation should be considered to look for synchronous DICER1-related disorders. In particular, abdominal ultrasound is recommended to exclude cystic nephroma and ovarian tumors (see genetic section).
DIAGNOSIS
Histology is mandatory and should especially distinguish PPB from benign conditions (congenital cystic adenomatoid malformations – CCAM, pulmonary sequestration and peripheral bronchogenic cysts, lung cysts) and other tumors (solid lung tumor of childhood, inflammatory myofibroblastic tumor, rhabdomyosarcoma) [HR]. A revision of the histological slides from a pathologist with proved experience in pediatric tumors and especially in PPB and/or pediatric sarcoma is highly recommended.

There are not tumor markers available.

TREATMENT:
- Multidisciplinary team discussion is mandatory at diagnosis and during therapy[HR].
- Patients/families should be proposed the enrolment in a prospective trial if available and data collection in national or international databases[HR].

Surgery
A surgical procedure is necessary to obtain a tumor sample and establish the diagnosis of PPB. Different series, although with a limited number of patients, have shown that tumor complete resection is a major prognostic factor (10, 12,13). Therefore, surgery represent a fundamental to establish the diagnosis and for the treatment for children with PPB.

Surgical procedure should be done after a radiological assessment that must include chest CT scan [HR]. Surgery planning should take into account the respiratory difficulties that patients with PPB generally present. Special attention is required due to mediastinal compression when general anaesthesia is needed especially at diagnosis[HR]. Management of any pneumothorax or pleural effusion should be done initially [HR]. It is recommended to avoid leaving a chest tub in order to minimize the contamination of the pleura [P].

Type I PPB
- I type I PPB a cystic pulmonary lesion is evident and should be suspected (especially if there is known familial history of DICER1 disease).
- A tumor total resection with a conservative intent should be planned.
- The recommended surgical approach is through a thoracotomy[HR]. Thoracoscopic approach is discouraged [P].
- A total pneumonectomy is not recommended [HR].
- When the number and localization of cysts preclude a complete resection, it is recommended to remove the largest cysts, and follow up closely the patients. In these cases, adjuvant chemotherapy might be considered to avoid the progression of a possible type I PPB to type II or III.
- The operative report should mention any mediastinal, diaphragmatic or pleural extension, clearly state the resection status and any rupture of the lesion [HR].
NB: Surgery that allows a complete resection of the tumor, after core needle biopsy (< 18 G) or fine needle aspiration, should be considered as a definitive R1 resection. Initial intra-thoracic cyst puncture should also be defined as R1 procedure provided that the entire tumor is then completely resected. In case of macroscopic incomplete surgery (R2 resection), new resection should be planned [R].

**Types II-III PPB**

- Types II-III usually present as a large pulmonary mass sometime with cystic changes. If not amenable to complete resection, an initial biopsy to allow histological examination before neoadjuvant therapy is recommended [HR].
- Core-needle (18 or 16 Gauge) or open surgical biopsies are both possible options, but they must be large enough to allow histological, biological and genetic tests. Cytology of pleural fluid cannot be used for diagnosis [HR].
- **Primary tumor resection** should only be considered in small tumors that can be easily and completely resected without any functional consequences, and if there is no clear radiological evidence of lymph node or metastatic disease. In all other cases, tumor resection should be considered after neo-adjuvant chemotherapy.
- Pneumonectomy to obtain radical tumor resection is discouraged at diagnosis [R].
- In case of life-threatening situation, up-front surgery may be discussed in order to allow, if possible, a complete resection of the tumor. In this case, if a total pneumonectomy is the only way to remove all lesions, an immediate debulking surgery is preferable with a planned second look surgery after adjuvant chemotherapy in order to resect all remaining parts of the tumor [HR].
- After neoadjuvant chemotherapy, **second look surgery** is highly recommended (S).
- Even if CT scan after neoadjuvant chemotherapy is not able to identify residual lesion, delayed surgery or thoracoscopy is advised to confirm the absence of residual viable cells in resected lesions in order to guide the adjuvant radiotherapy schedule [R].
- During surgery, the pleural cavity and the pulmonary parenchyma should be carefully analysed. Remaining pleural effusion should be collected for cytological analysis [HR]. All remaining pleural or lung nodules should be resected or biopsied (the positioning of clips by an interventional radiologist prior the operation may be of help for the surgeon) [R]. Surgery could imply non-anatomical lung resection or lobectomy and associated removal of suspicious pericardium and/or diaphragm and/or parietal pleura.
- All tissues resected should be histologically analysed in order to define the adjuvant radiotherapy fields. If initial lesion or pre-operative lesion suggests that a total pneumonectomy after neoadjuvant chemotherapy could be required, it should be balanced with the possibilities of local treatment with radiotherapy [P].

- Total pleuro-pneumonectomy could be taken into account in the absence of tumor regression after chemotherapy that seems unresectable otherwise.
- In case of residual viable tumor incompletely resected despite a second look surgery [P] pneumonectomy or lung irradiation should be discussed and decided taking into account the long terms effects of the two procedures. If a complete pneumonectomy is chosen, a complete parietal pleurectomy should be associated [R].
Timing of delayed surgery: there are no data to support this decision but it seems sensible to evaluate tumor resectability after 3 to 6 cycles and discuss local control timing in multidisciplinary board.

Chemotherapy

PPB Type I
- Data to support the use of chemotherapy in this group of patients are controversial.
- Every effort should be done to obtain a R0 resection at diagnosis and avoid or minimize further treatment.
- Adjuvant therapy might discussed to avoid relapse and progression to types II-III. Chemotherapy regimens used in historical series report long term survivors treated with different regimens (IVA, VAC, VA) or without any chemotherapy (O). Expert propositions are indicated above (O).
- In case of R1 resection, chemotherapy is recommended if R0 resection could not be achieved with a new surgery.
- The option of R0 resection without adjuvant chemotherapy should be considered in particular in children < 12 months because the transformation in type II-III is extremely rare in this group (O).
- Radiotherapy is not recommended for PPB type I [HR].

PPB types II-III:
- The risk of relapse and metastatic dissemination advice the use of chemotherapy independently from the results of surgery.
- There is no agreement on the chemotherapy regimen. In the literature different regimen with evidence of tumor response have been described. These regimens are similar to those used against rhabdomyosarcoma: IVA, VAIA, IVADO. Expert propositions are indicated above (O).
- There are no data about the optimal length of chemotherapy.
- An approach similar to the one used for soft tissue sarcoma seems advisable.
- In consideration of the higher risk of hepatic and renal toxicity specific attentions should be paid to the management of chemotherapy in very young infants: central venous access insertion, dose reduction according age and weight with slow increasing of doses after initial cycles [HR].

Metastatic PPB: Data are scarce. Expert opinion recommend the use of intensive chemotherapy, surgery (including neurosurgery for CNS metastasis), followed by radiotherapy to the primary tumor and metastatic site if feasible.
**Poorly responding tumors:** The experience on those patients is very limited. A different regimen should be tested, including anthracyclines if not used during first line chemotherapy.

**Relapsed tumors:** Survival is very poor for these patients. No specific second line treatment is supported by literature data. Antineoplastic agents that have been reported in the literature include etoposide and cisplatin or carboplatin. Overall drugs used for pediatric soft tissue sarcoma may be considered.

**Radiotherapy**
- The role of external radiotherapy is unclear in PPB [HR]. Recommendation is to deliver radiotherapy only in the case of residual viable tumor after chemotherapy and second look surgery. In this case the advantages and risks of the external radiotherapy should be balanced with a total pleuro-pneumonectomy.
- No data exist on the optimal dose of RT. A soft tissue sarcoma approach may be adopted.
- Total dosage should be between 45 Gy (R1 margins) to 54 Gy (R2 margins), with 1.8 Gy daily fractions [P]. Fields should therefore be focused and restricted to residual tumor volume after chemotherapy [P].
- Even in case of initial pleural effusion at diagnosis, in the absence of remaining pleural tumor cells after chemotherapy during the second look surgery, radiotherapy on the hemi-thorax may be avoid [P].

- Unilateral thorax irradiation may be restricted only to old patients with remaining pleural “viable” tumor that could not be resected during the second look surgery [R]. Specific attention should be done to myocardial irradiation after anthracyclin exposure. MDT discussion should balance irradiation risks with those of a total pleuro-pneumonectomy [HR].

**Genetic testing**
- *DICER1* mutation have been reported in approximately 2/3 of PPB patients analysed (6)
- Genetic counselling should be proposed to all patients with PPB and their family
- There are no surveillance guidelines for patients with PPB and *DICER1* mutations
- Patients with a PPB should have a genetic consuelling in order to screen all diseases associated with *DICER1* mutation [HR].
- Radiological and clinical screenings in case of constitutional *DICER1* mutation recommendations are not validate.
As overall recommendations, patients with constitutional DICER1 mutation may have [P]:
- Chest X-Ray at birth, then every 4 months until 6 years with an additional low dose thoracic CT scan at 6 months of age,
- Abdominal pelvic and abdominal US at birth for all, and every year in female since 10 years of age,
- Parental information about early consultation in case of precious puberty and occurrence of an abdominal mass and education about sinus or nasal masses (NCMH) or eye tumors (CBME).
- Clinical cervical examination every year, Cerebral MRI only in presence of clinical signs.
- Thyroid palpation yearly, with consideration of Thyroid US yearly.

Main open questions in the treatment of PPB patients

- Role of adjuvant chemotherapy in type I PPB
- Role of doxorubicin in type II-III PPB
- Role of RT in patients with type II-III with residual disease after surgery
- Indications and dose of radiotherapy
- Treatment of poor responding, metastatic and relapsed tumors
- Efficacy of new drugs for PPB patients
Even if many aspects of PPB treatment could not be fully supported by evidence-based medicine, EXPeRT group proposes a possible overall strategy in order to help physicians to treat patients. This therapeutic strategy should nevertheless be debated locally during multidisciplinary team discussion.

**Therapy summary.** Abbreviations: R0, complete delayed surgery; R1, microscopic incomplete delayed surgery; R2, macroscopic incomplete delayed surgery. Ad-IVA: IVAdo/IVA or VAIA regimens.

**Chemotherapy Regimens**

**N.B.:** there is a 3 weeks interval between cycles for all the regimens described below.

**VA Regimen:**
Vincristine, actinomycin-D:

**VA regimen (Vincristine + Actinomycin-D)**

- **Vincristine**: 1.5 mg/m² on day 1, 8, 15, 21; max 2 mg; bolus injection, in 10 ml 0.9% Nacl.
- **Actinomycin-D**: 1.5 mg/m² on day 1 and day 21, IV in 10 ml G5% dextrose.
- **Total number of cycles**: 6 cycles.

**IVA regimen**

**IVA regimen (Vincristine + Actinomycin-D + Ifosfamide)**

- **Ifosfamide**: 3 g/m²/day on day 1 and 2, IV 3 hours (total: 6 g/m²/course).
- **Vincristine**: 1.5 mg/m² on day 1, (+ D8 and D15 for the 2 first courses) (max 2 mg) per dose; bolus injection, in 10 ml 0.9% Nacl.
- **Actinomycin-D**: 1.5 mg/m² on 1, IV in 10 ml G5% dextrose.

Interval between cycles: 21 days. Total number of cycles: 9 cycles.
A central line is essential and mandatory for the administration of hydration and uromitexan. Hyper-hydration (3 l/m²/d) and diuresis (75% of intake) should be strictly followed at diagnosis in the context of a respiratory distress with compressive pleural effusions.

**IVADo regimen**

![IVADo regimen diagram](image)

**Figure 2.** Overall strategy in types II-III PPB with IVaDo/IVA (Expert regimen)

**Ifosfamide:** 3 g/m²/day on day 1 and 2, IV 3 hours (total: 6 g/m²/course).

**Vincristine:** 1.5 mg/m² on day 1, (+ D8 and D15 for the 2 first courses) (max 2 mg) per dose; bolus injection, in 10 ml 0.9% Nacl.

**Actinomycin-D:** 1.5 mg/m² on day 1 IV in 10 ml G5% dextrose.

**Doxorubicin:** 30 mg/m²/day on day 1 and 2 in 0.9% saline IV 4 hours. Maximum: 4 cycles

Interval between cycles: 21 days. Total number of cycles: 9 cycles.

A central line is essential for the administration of hydration and uromitexan and doxorubicin. Hyper-hydration (3 l/m²/d) and diuresis (75% of intake) should be strictly followed at diagnosis in the context of a respiratory distress with compressive pleural effusions.

**VAIA regimen**

p. 14
Figure 3. Overall strategy in types II-III PPB with VAIA (GPOH regimen)

**Ifosfamide**: 3 g/m²/day on day 1 and 2, IV 3 hours (total: 6 g/m²/course).

**Vincristine**: 1.5 mg/m² on day 1, (+ D8 and D15 for the 2 first courses) (max 2 mg) per dose; bolus injection, in 10 ml 0.9% Nacl.

**Actinomycin-D**: 1.5 mg/m² on day 1, IV in 10 ml G5% dextrose.

**Doxorubicin**: 40 mg/m²/day on day 1 and 2 in 0.9% saline IV 4 hours. Maximum 4 cycles

Interval between cycles: 21 days. Total number of cycles: 9 cycles.

A central line is essential and mandatory for the administration of hydration and uromitexan.

**Modification by age and weight:**

Vincristine and Actinomycin-D

- *For children < 3 months or < 5 kg*: 25 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance 33 µg/kg/injection for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg;

- *For children 3-6 months and 5-8 kg*: 33 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance 40 µg/kg/injection for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg;
- **For children 6-12 months and 8-10 kg:** 40 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance **50 µg/kg/injection** for further injections until age > 12 months and weight > 10 kg.

Ifosfamide

No alkylating agent before the age of 1 month

- **For children 1-3 months or < 5 kg:** 40 mg/kg/injection/d for the 2 first cycles (2 injections) then if good tolerance **60 mg/kg/injection/d** for further injections and 80 mg/kg/injection/d only when age > 6 months and weight > 8 kg;

- **For children 3-6 months and 5-8 kg:** 60 mg/kg/injection/d for the 2 first cycles (2 injections) then if good tolerance **80 mg/kg/injection/d** for further injections and 100 mg/kg/injection/d only when age > 6 months and weight > 8 kg;

- **For children 6-12 months and 8-10 kg:** 80 mg/kg/injection/D for the 2 first cycles (2 injections) then if good tolerance **100 mg/kg/injection/d** for further injections until age > 12 months and weight > 10 kg;

- **For children > 12 months and > 10 kg:** **3000 mg/m²/injection/d**.

Doxorubicin (in IVADo Regimen)

- **For children < 3 months or < 5 kg:** No doxorubicin

- **For children 3-6 months and 5-8 kg:** 0.6 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **0.8 mg/kg/injection** for further injections and 1 mg/kg/injection only when age > 6 months and weight > 8 kg;

- **For children 6-12 months and 8-10 kg:** 0.8 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1 mg/kg/injection** for further injections until age > 12 months and weight > 10 kg;

- **For children > 12 months and > 10 kg:** **30 mg/m²/injection/day**.

Doxorubicin (in VAIA Regimen)

- **For children < 3 months or < 5 kg:** No doxorubicin

- **For children 3-6 months and 5-8 kg:** 0.85 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1 mg/kg/injection** for further injections and 1 mg/kg/injection only when age > 6 months and weight > 8 kg;

- **For children 6-12 months and 8-10 kg:** 1 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1.33 mg/kg/injection** for further injections until age > 12 months and weight > 10 kg;
- For children > 12 months and > 10 kg: 40 mg/m²/injection/day.

References


Coordinators: Daniel Orbach, M.D (Pediatric-adolescent-young adult department, Institut Curie, Paris, France), Gianni Bisogno, M.D, Ph.D (Pediatric Hematology and Oncology Division, Padova University, Padova, Italy),

EXPERT member:

Working Group: Sabine Sarnaeki, M.D, Ph.D (Department of Pediatric Surgery, Hôpital Necker-Enfants-Malades and Assistance Publique Hôpitaux de Paris, Université Paris Descartes, Paris, France), Teresa Stachowicz-Stencel, M.D (Department of Pediatrics, Medical University, Gdansk, Poland), M Gauthier-Villars, M.D (Genetic department, Institut Curie, Paris, France), S Helfre, M.D (Radiotherapy department, Institut Curie, France), F Hameury, M.D (IHOP, Lyon, France), V Minard-Colin, M.D,Ph. D (pediatric department, Gustave Roussy, Villejuif, France).

External advisors: Ewa Koscielniak (CWS Study Group, GPOH, Germany). Yoav Messinger (IPPB Registry, USA)