nisation against CMV infection. They are used prophylactically, especially in patients undergoing certain transplant procedures. In transplants from CMV-seropositive donors into seronegative recipients, prophylactic use of cytomegalovirus immunoglobulin with ganciclovir should also be considered.

In the USA, a cytomegalovirus immunoglobulin G is available for use in recipients of heart, kidney, liver, lung, and pancreas transplants, and for CMV-seronegative recipients of these organs other than kidney from CMV-seropositive donors. The dosage schedule for kidney transplant recipients is 150 mg/kg by intravenous infusion within 72 hours of transplantation, then 100 mg/kg once every 2 weeks for 4 doses, then 50 mg/kg every 4 weeks for 2 doses. The rate of infusion should start at 15 mg/kg per hour increasing gradually to a maximum rate of 60 mg/kg per hour. For recipients of transplants other than kidney, the recommended dosage schedule is 150 mg/kg within 72 hours of transplantation and then once every 2 weeks for 4 further doses, then 100 mg/kg every 4 weeks for 2 doses. In the UK, cytomegalovirus immunoglobulin is available on a named patient basis for prophylaxis in patients receiving immunosuppressive treatment.

The name sevirumab is applied to a χ-chain human monoclonal cytomegalovirus immunoglobulin G1.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: CytoGam†; Megalotect; ***Austral.:*** CMV Immunoglobulin; ***Austria:*** Cytoglobin; Cytotect; ***Belg.:*** Ivegam-CMV; ***Chile:*** Cytotect; ***Cz.:*** Cytotect; ***Ger.:*** Cytoglobin; Cytotect; ***Gr.:*** Megalotect; ***Hong Kong:*** Cytotect; ***Hung.:*** Cytotect; ***Irl.:*** Megalotect†; ***Israel:*** Megalotect; ***Ital.:*** Cytotect; Immunoendocig†; Uman-Cig†; ***Neth.:*** Megalotect; ***Pol.:*** Cytotect; ***Port.:*** Megalotect; ***S.Afr.:*** Megalotect†; ***Singapore:*** Megalotect; ***Switz.:*** Cytotect; ***Thai.:*** Megalotect; ***Turk.:*** Cytotect; ***USA:*** CytoGam.

Cytomegalovirus Vaccines

Vacunas contra el citomegalovirus.

Profile

Several vaccines for active immunisation against CMV infection are under investigation, including some produced by recombinant technology. A live attenuated cytomegalovirus vaccine containing human CMV Towne strain has been investigated in humans since the late 1970s, particularly for the prevention of CMV infection in renal transplant recipients. However, there have been doubts over its safety.

◊ Several promising candidate vaccines against human CMV infection are under development, of which 5 have been or are being tested in humans.[1] Firstly, attenuated CMV (Towne strain) vaccine has been tried but found to be erratic in efficacy and loses segments of its genetic material; to overcome this a second, more robust, vaccine has been designed consisting of a chimera between the attenuated CMV and wild-type virus. The third vaccine developed, known as ALVAC, consists of a canarypox vector with either a glycoprotein B envelope or a core antigen from CMV pp65, a protein found to be recognised by CD8+ T lymphocytes during naturally acquired infection. Fourthly, a protein sub-unit vaccine consisting of a recombinant envelope glycoprotein has been found to be safe and to induce a neutralising antibody response. Finally, the fifth vaccine developed is a mixture of synthetic peptides incorporating a T helper epitope known as CD8+ cytotoxic T cell epitope and a lipid tail. Currently, the attenuated cytomegalovirus vaccine, the protein sub-unit vaccine, and the recombinant vector vaccine have been or are being tested in CMV-negative subjects, and the chimeric vaccine has been tested in CMV-positive patients as a precursor to testing in CMV-negative persons.[1]

Further vaccine candidates that have been proposed include DNA vaccines and a vaccine based on recombinant technology.[1] Some commentators[2] have suggested that reduction or prevention of cytomegalovirus disease may be a more realistic goal for a vaccine than prevention of infection.

1. Arvin AM, *et al.* Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004; **39:** 233–9.
2. Khanna R, Diamond DJ. Human cytomegalovirus vaccine: time to look for alternative options. *Trends Mol Med* 2006; **12:** 26–33.

Dengue Fever Vaccines

Vacunas del dengue.

Profile

Live attenuated vaccines under study for active immunisation against dengue fever contain dengue virus types 1, 2, 3, and 4 alone or in various combinations. WHO considers that protection against only one or two dengue viruses might actually increase the risk of more serious disease. The ultimate aim is to produce a vaccine active against all types of dengue virus.

Recombinant vaccines are also under investigation.

◊ References.

1. Velzing J, *et al.* Induction of protective immunity against dengue virus type 2: comparison of candidate live attenuated and recombinant vaccines. *Vaccine* 1999; **17:** 1312–30.
2. Kanesa-Thasan N, *et al.* Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine* 2001; **19:** 3179–88.
3. Rothman AL, *et al.* Induction of T lymphocyte responses to dengue virus by a candidate tetravalent live attenuated dengue virus vaccine. *Vaccine* 2001; **19:** 4694–99.
4. Sabchareon A, *et al.* Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. *Am J Trop Med Hyg* 2002; **66:** 264–72.
5. Sun W, *et al.* Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. *Am J Trop Med Hyg* 2003; **69** (suppl 6): 24–31.
6. Sabchareon A, *et al.* Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J* 2004; **23:** 99–109.
7. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. *N Engl J Med* 2007; **357:** 2222–5.
8. Edelman R. Dengue vaccines approach the finish line. *Clin Infect Dis* 2007; **45** (suppl 1): S56–60.
9. Hatch S, *et al.* Dengue vaccine: opportunities and challenges. *IDrugs* 2008; **11:** 42–5.

Dental Caries Vaccines

Vacunas de la caries dental.

Profile

Dental caries vaccines consisting of purified proteins from *Streptococcus mutans* or *Str. sobrinus* are under investigation. Monoclonal antibodies are also being studied for local passive immunisation.

◊ Several *animal* studies of candidate vaccines for the prevention of dental caries have shown that immunisation with protein antigens from *Streptococcus mutans* or *Str. sobrinus* can induce salivary IgA antibodies which inhibit both sucrose-dependent or sucrose-independent accumulation of these organisms on tooth surfaces. It is thought that candidate vaccines for study in humans could be given by mucosal application since children are already naturally exposed to the antigens involved during the first years of life. Infection with *Str. mutans* normally occurs from the age of about 18 months and the intention is therefore to vaccinate 1-year-old children in order to intercept colonisation. However, progress towards a vaccine for active immunisation against dental caries requires further clinical evaluation. Passive administration of salivary antibodies to *Str. mutans* has also provided some protection in preclinical studies and small scale studies in humans.[1-4]

1. Koga T, *et al.* Immunization against dental caries. *Vaccine* 2002; **20:** 2027–44.
2. Smith DJ. Caries vaccines for the twenty-first century. *J Dent Educ* 2003; **67:** 1130–9.
3. Russell MW, *et al.* A caries vaccine? The state of the science of immunization against dental caries. *Caries Res* 2004; **38:** 230–5.
4. Smith DJ, Mattos-Graner RO. Secretory immunity following mutans streptococcal infection or immunization. *Curr Top Microbiol Immunol* 2008; **319:** 131–56.

Diphtheria Antitoxins

Antitoxinas diftéricas.

ATC — J06AA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria Antitoxin; Immunoserum Diphtherici). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Corynebacterium diphtheriae*. It has a potency of not less than 1000 international units/mL when obtained from horse serum and not less than 500 international units/mL when obtained from other mammals. It should be stored at 2° to 8°, and not be allowed to freeze.
The BP 2008 states that Dip/Ser may be used on the label.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Diphtheria antitoxins neutralise the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection. An antibacterial is usually given concomitantly (see p.168). Diphtheria antitoxin is generally not used for the prophylaxis of diphtheria because of the risk of provoking a hypersensitivity reaction. Contacts of a diphtheria case should be promptly investigated, given antibacterial prophylaxis and active immunisation with a suitable diphtheria-containing vaccine as appropriate (see below), and kept under observation.

A test dose of diluted diphtheria antitoxin should always be given intradermally to exclude hypersensitivity. In the UK, diphtheria antitoxin is given by intravenous infusion for the treatment of diphtheria of mild to moderate severity in the following recommended doses: for nasal diphtheria, 10 000 to 20 000 units; for tonsillar diphtheria, 15 000 to 25 000 units; for pharyngeal or laryngeal diphtheria, 20 000 to 40 000 units. In cases of combined disease, or when diagnosis is delayed, 40 000 to 60 000 units should be given, and, in severe disease, doses up to 100 000 units used. For most cutaneous infections, diphtheria antitoxin is insufficiently absorbed and is therefore not given; however, if the ulcer is sufficiently large (more than 2 cm^2) and especially if it is membranous, then 20 000 to 40 000 units may be given. Higher doses have been used in some countries.

Preparations

Ph. Eur.: Diphtheria Antitoxin.

Diphtheria Vaccines

Vacunas de la difteria.

ATC — J07AF01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed); Vaccinum Diphtheriae Adsorbatum). A preparation of diphtheria formol toxoid adsorbed on a mineral carrier. The formol toxoid is prepared from the toxin produced by the growth of *Corynebacterium diphtheriae*. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives, particularly those of the phenolic type. It contains not less than 30 international units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed, Reduced Antigen Content); Vaccinum Diphtheriae, Antigeniis Minutum, Adsorbatum). It is an adsorbed diphtheria vaccine containing not less than 2 international units per dose.
The BP 2008 states that for a vaccine for use in the UK, the amount of toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents per dose.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Local reactions may occur but are generally not severe in young children; the frequency and severity of reactions is reported to be less in children under 2 years of age than in older children and adults. If diphtheria vaccines or vaccines containing a diphtheria component need to be given to children over the age of 10 years or to adults, vaccines with a reduced content of diphtheria toxoid and intended for adults and adolescents should be used. For further details see Uses and Administration, below.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Diphtheria vaccines are used for active immunisation against diphtheria. The non-adsorbed vaccine has poor immunogenic properties and its effects are enhanced if given as an adsorbed preparation. For primary immunisation combined diphtheria vaccines, usually diphtheria, tetanus, and pertussis vaccines (p.2210) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p.2212), are used. A single-component diphtheria vaccine has sometimes been used, for example in the event of contact with an infected patient or a carrier. For discussion of immunisation schedules, see under Vaccines, p.2202.

Individuals coming into contact with a case of diphtheria or carrier of a toxigenic strain, or those travelling to an endemic or epidemic area should receive a complete primary course or a reinforcing dose according to age and immunisation history; those not previously immunised should receive a primary course of immunisation, and those previously immunised should receive a single reinforcing dose of a diphtheria-containing vaccine. Contacts of a case of diphtheria or carrier of a toxigenic strain should in addition receive a prophylactic course of a suitable antibacterial (see p.168). Individuals at repeated risk of exposure to infection may be offered booster doses every 10 years.

Schick testing (p.2384) to ascertain immune status is no longer considered necessary before giving diphtheria vaccine to adults provided that a low dose is given; antibody testing is used to check immunity in those regularly exposed to diphtheria.

In some countries, booster doses of a diphtheria and tetanus vaccine are recommended every 10 years (see under Diphtheria and Tetanus Vaccines, p.2210).

Conjugation to diphtheria toxoid has been used to increase the immunogenicity of other vaccines (see Haemophilus Influenzae Vaccines, p.2213).

Preparations

Ph. Eur.: Diphtheria Vaccine (Adsorbed); Diphtheria Vaccine (Adsorbed, Reduced Antigen Content).

Proprietary Preparations (details are given in Part 3)
Cz.: Aldiana†; ***NZ:*** Di Anatoxal.

Diphtheria and Tetanus Vaccines

Vacunas de la difteria y el tétanos.

ATC — J07AM51.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed); Vaccinum Diphtheriae et Tetani Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid adsorbed on a mineral carrier. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid and not less than 40 international units of tetanus toxoid per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DT/Vac/Ads(Child) may be used on the label.

The BP 2008 gives Adsorbed Diphtheria-Tetanus Prophylactic as an approved synonym.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae et Tetani, Antigeni-o(-is) Minutum). It is diphtheria and tetanus vaccine (adsorbed) containing not less than 2 units of diphtheria toxoid and not less than 20 units of tetanus toxoid per dose.

The BP 2008 states that for a vaccine for use in the UK, the amount of diphtheria toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents of diphtheria toxoid per dose.

The BP 2008 states that dT may be used on the label.

USP 31 (Diphtheria and Tetanus Toxoids Adsorbed). A sterile suspension prepared by mixing suitable quantities of plain or adsorbed diphtheria toxoid and plain or adsorbed tetanus toxoid and, if plain toxoids are used, an aluminium adsorbing agent. The antigenicity or potency and the proportions of the toxoids are such as to provide an immunising dose of each toxoid in the labelled dose. It should be stored at 2° to 8° and not be allowed to freeze.

USP 31 (Tetanus and Diphtheria Toxoids Adsorbed for Adult Use). A sterile suspension prepared by mixing suitable quantities of adsorbed diphtheria toxoid and adsorbed tetanus toxoid using the same precipitating or adsorbing agent for both toxoids. The antigenicity or potency and the proportions of the toxoids are such as to provide, in the labelled dose, an immunising dose of adsorbed tetanus toxoid and one-tenth of the immunising dose of adsorbed diphtheria toxoid specified for children and not more than 2 Lf of diphtheria toxoid. It should be stored at 2° to 8° and not be allowed to freeze.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, above, and Tetanus Vaccines, p.2240. Diphtheria and tetanus vaccines are reported to produce fewer adverse effects than diphtheria, tetanus, and pertussis vaccines (see under Incidence of Adverse Effects, p.2210).

Dose-related effects. A high incidence of adverse effects was reported in teenagers inadvertently given a high-dose diphtheria and tetanus vaccine intended for use in infants.[1] Most reactions were classified as mild or moderately severe, but severe local or systemic reactions occurred in a third of those reporting reactions.

1. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996; **313:** 533–4.

Effects on the nervous system. Encephalopathy more commonly follows vaccination with diphtheria, tetanus, and pertussis vaccine than with diphtheria and tetanus vaccine (p.2210). Several cases of encephalopathy occurred in a small region in Italy in children after immunisation against diphtheria and tetanus,[1] although it was not possible to infer a causal relationship. A case of polyradiculoneuritis has been reported in a patient after the use of a diphtheria-tetanus vaccine and was considered most likely to have been due to the tetanus component.[2]

1. Greco D. Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy. *Bull WHO* 1985; **63:** 919–25.
2. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol* 1983; **40:** 56–7.

GUILLAIN-BARRÉ SYNDROME. Evidence mainly from case reports and uncontrolled studies favoured a causal relationship between vaccination with diphtheria and tetanus vaccines or single-antigen tetanus vaccines and Guillain-Barré syndrome. The data came primarily from immunocompromised patients.[1] However, a later analysis of active surveillance epidemiological studies of Guillain-Barré syndrome and tetanus vaccination history concluded that if an association exists, it must be extremely rare and not of public health significance.[2]

1. Stratton KR, *et al.* Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine. *JAMA* 1994; **271:** 1602–5.
2. Tuttle J, *et al.* The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997; **87:** 2045–8.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Combined adsorbed diphtheria and tetanus vaccines may be used for active immunisation, although vaccines used for primary immunisation usually combine diphtheria, tetanus, and pertussis, and sometimes also Haemophilus influenzae and poliomyelitis. Diphtheria and tetanus vaccines are used in some countries for reinforcing doses after primary immunisation; in the USA they are given to adults every 10 years. For discussion of immunisation schedules, see under Vaccines, p.2202.

The non-adsorbed combined diphtheria and tetanus vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Booster doses. In many countries, booster doses of combined diphtheria and tetanus vaccines are recommended every 10 years, and studies have been conducted to assess whether this is necessary. Since the incidence of clinical diphtheria in many countries in western Europe and North America approaches zero, it had been considered that there was no need for booster doses in adults, despite low antibody titres, so long as the policy of immunisation during infancy was maintained.[1,2] However, after a report[3] of an outbreak of clinical diphtheria in Sweden after a period of many years during which no indigenous cases of diphtheria had occurred and the disease was regarded as being eliminated from the country, the question of immunity in adults and the need for revaccination again arose. In the USA, it was considered[4] that re-immunisation every 10 years with a diphtheria and tetanus combined vaccine was mandatory and that this combined vaccine should be used whenever a tetanus vaccine was indicated as in treating emergency wounds. This policy is also adopted in the UK. Outbreaks of diphtheria in Russia and neighbouring countries[5] have prompted recommendations for booster doses in travellers to these countries.

1. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985; **i:** 1089–91.
2. Anonymous. Diphtheria and tetanus boosters. *Lancet* 1985; **i:** 1081–2.
3. Rappuoli R, *et al.* Molecular epidemiology of the 1984–1986 outbreak of diphtheria in Sweden. *N Engl J Med* 1988; **318:** 12–14.
4. Karzon DT, Edwards KM. Diphtheria outbreaks in immunized populations. *N Engl J Med* 1988; **318:** 41–3.
5. Anonymous. Diphtheria immunisation—advice from the Chief Medical Officer. *Commun Dis Rep* 1993; **3:** 27.

Preparations

Ph. Eur.: Diphtheria and Tetanus Vaccine (Adsorbed); Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content);
USP 31: Diphtheria and Tetanus Toxoids Adsorbed; Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.

Proprietary Preparations (details are given in Part 3)
Arg.: Diftavax†; DT Vax†; Imovax DT; Vacuna Doble; ***Austral.:*** ADT; CDT; ***Austria:*** DT-reduct; Td-pur; ***Belg.:*** Ditemer†; Tedivax; ***Braz.:*** Dif-Tet-All; DT Vax†; Refortrix†; ***Canad.:*** Td Adsorbed; ***Cz.:*** Alditeana†; ***Denm.:*** DiTe Booster; ***Fin.:*** DiTe Booster; ***Ger.:*** DT-Impfstoff†; Td-Impfstoff; Td-pur; Td-Rix; ***Gr.:*** Anatoxal Di Te Berna†; DT Vax; ***Hong Kong:*** DiTe Anatoxal†; ***India:*** DT-Vac; Dual Antigen; ***Irl.:*** Diftavax; ***Ital.:*** Anatoxal Adulti; Dif-Tet-All; Diftavax; Ditanrix; ***Malaysia:*** Di Te Anatoxal†; ***Norw.:*** DiTe Booster; ***NZ:*** ADT; CDT; DiTe Anatoxal; ***Philipp.:*** Di Te Anatoxal; ***Pol.:*** DT; ***S.Afr.:*** DT Vax; ***Singapore:*** Di Te Anatoxal†; ***Spain:*** Anatoxal Di Te†; Anatoxal Te Di; Diftavax; Ditanrix; TD; ***Swed.:*** DiTe Booster; ***Switz.:*** Anatoxal Di Te; Ditanrix; ***Thai.:*** Adsorbed DT Vaccine; Di Te Anatoxal†; Dif-Tet-All†; DT Vax†; ***Turk.:*** Di Te Anatoxal; ***UK:*** Diftavax†; ***USA:*** Decavac.

Diphtheria, Tetanus, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos y Haemophilus influenzae.

Profile

Combined adsorbed diphtheria, tetanus, and *Haemophilus influenzae* type b vaccines have been used in some countries for active immunisation of infants. For discussion of immunisation schedules see under Vaccines, p.2202. For concern over the antigenicity of *Haemophilus influenzae* type b vaccine in combined vaccines, see under Haemophilus Influenzae Vaccines, Interactions, p.2213.

Diphtheria, Tetanus, and Hepatitis B Vaccines

ATC — J07CA07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, and hepatitis B vaccines have been used in some countries for active immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Gr.: Primavax†.

Diphtheria, Tetanus, and Pertussis Vaccines

Vacunas de la difteria, el tétanos y la tos ferina.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid on a mineral carrier to which a suspension of killed *Bordetella pertussis* has been added. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid, not less than 40 international units if the test is performed in *guinea-pigs*, or 60 international units if the test is performed in *mice*, of tetanus toxoid, and not less than 4 international units of the pertussis component per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DTwP may be used on the label.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Sine Cellulis ex Elementis Praeparatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP2008 states that DTaP may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, p.2209, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

The incidence of local reactions and fever is reported to be lower with the current accelerated immunisation schedules than the formerly used schedules spreading primary immunisation over 6 months. Local reactions and pyrexia occur less commonly after acellular pertussis vaccines than whole-cell pertussis vaccines, especially in children older than 6 months.

In infants with a personal or close family history of seizures, precautions should be taken to avoid pyrexia. See under Pertussis Vaccines for further details of precautions and contra-indications in individuals with a history of neurological problems.

Incidence of adverse effects. The incidence of local reactions is lower with diphtheria and tetanus vaccines combined with an acellular pertussis component (acellular DTP) than with a whole-cell pertussis component, and is similar to that after diphtheria and tetanus (DT) vaccines. Such reactions are generally mild and self-limiting. Rarely, high fever, persistent or inconsolable crying (possibly as a reaction to pain), hypotonic-hyporesponsive collapse, or short-lived convulsions (frequently febrile convulsions) may occur, and have been reported after both DT and acellular DTP vaccines with equal frequency. These reactions do not appear to have any long-term consequences. Rare but serious acute neurological complications including encephalopathy and prolonged seizures have been reported after DTP vaccines and have been attributed to the whole-cell pertussis component (see Effects on the Nervous System, p.2230) but the association could be coincidental. Epidemiological studies have shown that such events are exceedingly rare and only occasionally followed by long-term neurological damage. Analysis of these studies has been difficult but authorities in the UK and USA concluded that the evidence was insufficient for a link.

A causal relationship between DTP vaccination and sudden infant death syndrome (SIDS) has not been established and any temporal relationship is likely to be due to chance.[1,2] There is evidence that the risk of SIDS is lower in infants who have been vaccinated.[3]

Immediate anaphylactic reactions have been reported and are regarded as a contra-indication to further use of DTP vaccine. However, the appearance of a rash is not generally regarded as a contra-indication to further doses.