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Contemporary Review

Considerations for setting occupational exposure limits for novel pharmaceutical modalities

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ABSTRACT

In order to develop new and effective medicines, pharmaceutical companies must be modality agnostic. As science reveals an enhanced understanding of biological processes, new therapeutic modalities are becoming important in developing breakthrough therapies to treat both rare and common diseases. As these new modalities progress, concern and uncertainty arise regarding their safe handling by the researchers developing them, employees manufacturing them and nurses administering them. This manuscript reviews the available literature for emerging modalities (including oligonucleotides, monoclonal antibodies, fusion proteins and bispecific antibodies, antibody-drug conjugates, peptides, vaccines, genetically modified organisms, and several others) and provides considerations for occupational health and safety-oriented hazard identification and risk assessments to enable timely, consistent and well-informed hazard identification, hazard communication and risk-management decisions. This manuscript also points out instances where historical exposure control banding systems may not be applicable (e.g. oncolytic viruses, biologics) and where other occupational exposure limit systems are more applicable (e.g. Biosafety Levels, Biologic Control Categories).

1. Introduction

Until recently, small molecule drugs were the primary focus of the pharmaceutical industry. As the scientific field advances through an enhanced understanding of biological processes, the role of genetics and the interplay among peptides/DNA/RNA, and how these interactions relate to both the cause and cure of disease, many new therapeutic modalities are becoming important in developing breakthrough therapies to treat both rare and common diseases. In addition to novel modalities, increasingly potent and persistent medicines are being designed to enable lower doses and less frequent dosing. As compounds become more potent, even seemingly small amounts of dermal or inhalation exposure can pose significant health hazards to the employee who is synthesizing and manufacturing the drug, to the health care worker who is administering the drug, to the patient performing self-administration (e.g. subcutaneous injection of protein therapeutics at home) and/or to others in the shared facilities, clinics, or homes where these activities are taking place. There have been several attempts to identify and communicate the hazards associated with drugs via the safety data sheet (SDS), Globally Harmonized System of Classification and Labelling of Chemicals (GHS) categorizations, and the National Institute for Occupational Safety and Health (NIOSH) hazardous drug list (Nations U, 2019; NIOSH, 2016). However, guidance is also needed for those preparing the SDSs and assigning hazard classifications.

As the bulk of novel modality pharmaceuticals being evaluated/developed are in the discovery phase of drug development, they tend to lack appreciable nonclinical and clinical data, including pharmacological potency and toxicity information. Compounds with limited data, such as those in early discovery research and development, are placed into occupational exposure control bands (ECBs; also commonly referred to as occupational exposure bands [OEBs] or occupational health categories [OHCs]). Occupational banding/categorization systems essentially pair a hazard determination with an acceptable occupational exposure concentration range along with appropriate exposure controls and handling practices. These bands are assigned based on historical experience and information, read-across strategies, *in silico* evaluations, *in vitro* screening data, and *in vivo* data (where available) conducted to elucidate a compound's pharmacological and/or toxicological characteristics and subsequent hazard assumptions and classifications.

What follows is an overview of occupational hazards and risks associated with several of the most broadly utilized pharmaceutical modalities. Literature searches were conducted to identify key

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Abbreviations:

aa	amino acid
AAV	adeno-associated virus
ADA	Anti-drug antibody
ADC	antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
ADME	adsorption, distribution, metabolism and elimination
ALL	acute lymphoblastic leukemia
ATC	adoptive T-cell therapy
ALARA	as low as reasonably achievable
APC	Antigen presenting cell
API	active pharmaceutical ingredient
ASO	antisense oligonucleotide
BA	bioavailability
BCC	biologic control category
BCMA	B-cell maturation antigen
BMS	Bristol-Myers Squibb
bsAb	bispecific antibody
BSL	biosafety level
CAR	chimeric antigen receptor
Cas9	CRISPR associated protein 9
CBI	cyclopropabenzidole
CD	cluster of differentiation
CDC	Centers for Disease Control
CDC	complement dependent cytotoxicity
CNS	central nervous system
COVID	coronavirus disease
CRISPR	clustered regularly interspaced short palindromic repeats
CRS	cytokine release syndrome
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
CYP450	cytochrome P450
Da	Dalton
DAMP	damage-associated molecular pattern molecules
DAR	drug-to-antibody ratio
DM1	mertansine
DNA	deoxyribonucleic acid
DSEN	dermal sensitizer notation
E −	early
E2F	E2 factor
ECB	exposure control band
EG	exposure guideline
EGFR	epidermal growth factor receptor
EpCAM	epithelial cell adhesion molecule
EpoFc	erythropoietin-Fc fusion molecule
Fab	antigen binding fragment
Fc	crystallizable fragment
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FPF	fine particle fraction
FIXa	factor IXa
FX	factor X
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GM	genetically modified
GM-CFS	granulocyte-macrophage colony-stimulating factor
GSD	geometric standard deviation
h	hour
HBEL	health based exposure limit
HER2	human epidermal growth factor receptor 2
HSV-1	herpes simplex type 1
IC50	half maximal inhibitory concentration
ICH M7	International Council on Harmonization M7 guidance
Ig	immunoglobulin
i.t.	intratracheal
IV	intraveous
kDa	kilodalton
kg	kilogram
L	late
LAB	lactic acid bacteria
LAG-3	lymphocyte-activation gene-3
LBP	live bio-therapeutic product
LNA	locked nucleic acid
mAbs	monoclonal antibodies
MHC	major histocompatibility complex
MW	molecular weight
MMAD	mass median aerodynamic diameter
mg	milligram
mRNA	messenger ribonucleic acid
miRNA	micro ribonucleic acid
NET	neuroendocrine tumor
NIOSH	National Institute for Occupational Safety and Health
OEB	occupation exposure band
OEL	occupational exposure limit
ON	oligonucleotide
OSHA	Occupational Safety and Health Administration
PBD	pyrrolobenzodiazepines
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed death-1 cell surface membrane receptor
PD-L1	programmed death-ligand 1
PEG	polyethylene glycol
PET	positron-emission tomography
PK	pharmacokinetic
ppm	parts per million
pRb	retinoblastoma protein
PSA	prostate specific antigen
QC	quality control
QSAR	quantitative structure-activity relationships
RNA	ribonucleic acid
RNAi	RNA interference
Rnase H	ribonuclease H
SDS	Safety data sheet
SGN-35	auristatin
siRNA	small interfering
5 sc	exposure control band 5 special case
TCR	T cell receptor
T-DM1	maytansine
TIL	tumor-infiltrating lymphocyte
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
Tmax	the time after administration of a drug when the maximum plasma concentration is reached
TNF	tumor necrosis factor
TMDD	target-mediated drug disposition
TTC	threshold of toxicological concern
T-VEC	Talimogene laherparepvec
μg	microgram
UNA	unlocked nucleic acid
VLP	virus-like particle
WHO	World Health Organization

toxicology and pharmacology information on each of the modalities with a focus on occupationally relevant data including occupational exposure case studies and inhalation studies for the modalities described (See Supplementary Table 1). Information discussed for each modality includes:

(1) Background: a brief background on the modality;
(2) How they work: an introduction to how the drugs within this modality work;
(3) Marketed drugs: examples of marketed drugs;
(4) ADME: the documented absorption, distribution and elimination (ADME) properties;
(5) Health hazards associated with therapeutic use: health hazards observed or expected after therapeutic administration as well as those observed in relevant nonclinical studies;
(6) Occupational hazard and exposure considerations: a summary of the occupational exposure risk considerations and occupationally relevant hazards; and
(7) Occupational exposure banding guidance: a recommendation for an occupational exposure control band based on the occupational health hazards and risks.

This work provides guidance in regards to characterizing the occupational hazards of new and emerging modalities to enable timely, consistent and well-informed hazard identification, hazard communication and risk-management decisions.

2. Occupational exposure control banding

2.1. Background of occupational exposure control banding

The concept of using hazard-based categories to communicate potential occupational health concerns, signal workers and employers to the need for risk management, and inform exposure control requirements has been utilized for decades. The original occupational health categorization practices were developed in the pharmaceutical industry and such hazard classification and category-based systems are deeply embedded in occupational health and safety practices, particularly in the pharmaceutical industry (Naumann et al., 1996; Zalk and Nelson, 2008; NIOSH, 2019). Additionally, such systems are elements of well-developed, current hazard communication programs (e.g., United Nations 2019 Globally Harmonized System of Classification and Labelling of Chemicals) (Nations U, 2019). Occupational health categorization and compound handling practice systems are considered standard practice throughout the pharmaceutical industry in both research and manufacturing operations.

The occupational categorization system was designed to give guidance, based on historical experience, on safe handling practices for compounds with limited data as a stopgap until additional relevant data could be generated. For pharmaceuticals with robust data sets, compound-specific occupational exposure limits (OELs) are established to protect employees. However, when there is limited data for a compound, occupational exposure banding is often employed to establish occupational exposure constraints. While an OEL is a specific airborne concentration limit usually presented in units of $\mu g/m^3$ or parts per million (ppm), an occupational ECB is a range of airborne concentrations to which exposure to a compound should be controlled to ensure worker safety (See Table 1).

2.2. Application of occupational exposure control banding

Occupational exposure banding (also known as hazard banding or health hazard banding) is a systematic evaluation process utilized to assign chemicals/compounds to "bands" based on selected health effect endpoints (e.g. inherent toxicity, pharmacological effects, etc.). The basic premise of the ECB classification system is to place chemicals into categories based on their inherent toxicity and potency, which offers a simplified solution for controlling worker exposures to compounds in the workplace. Briefly, an initial hazard assessment is conducted in an effort to identify potential exposure ranges expected to represent negligible risk for the physical (e.g. corrosivity), toxicological, and/or pharmacological effect(s) of concern. The mechanism of pharmacological action, *in vitro/in vivo* potency, preclinical dose-response related effects, bioavailability (inhalation, oral and dermal), therapeutic dose,

Table 1
Example of an exposure control band (ECB) system.

ECB	Range ($\mu g/m^3$)[a]	Relevant Compounds	Rationale	Examples
1	≥1000	Compounds of very low toxicity/potency		Caffeine
2	100 - < 1000	Compounds of low toxicity/potency	Permitted exposure of >1000 μg/day (>1 mg/day) for compounds of low toxicity which are not potent. Compounds that may cause mild, reversible acute affects (e.g. skin/eye irritation).	Antibiotics of tetracycline, aminoglycoside and fluoroquinolones class; some cardiovascular, antiviral, and central nervous system (CNS) drugs
3	10 - < 100	Compounds of intermediate toxicity/ potency	A TTC of 1000 μg/day is recommended for relatively unstudied compounds that may be intermediately potent or toxic.	Some cardiovascular drugs, statins
4	1 - < 10	Potent/Toxic compounds	A TTC of 100 μg/day is recommended for relatively unstudied compounds that are not likely to be highly potent, highly toxic, or carcinogenic, have no *a priori* evidence of unusual potency or toxicity and are not considered mutagenic (Dolan et al., 2005; Kroes et al., 2004; Cramer et al., 1978; Bercu and Dolan, 2013).	Some potent cardiovascular, metabolic, antiviral and CNS drugs, early discovery APIs, some chemically synthesized peptides
5	0.1 - <1	Highly toxic/potent compounds	A TTC of 10 μg/day[b] is recommended for relatively unstudied compounds that may be highly potent or highly toxic with limited data to indicate they may produce pharmacologic or toxic effects at very low doses (Dolan et al., 2005; Kroes et al., 2004; Cramer et al., 1978).	Toxic oncology drugs, potent compounds, chemically synthesized peptides, antibody drug conjugates, steroids
5 special case	<0.1	Especially potent/toxic compounds	A TTC of 1 μg/day[b] is recommended in the absence of sufficient data for anti-cancer drugs, which are developmental toxicants, mutagenic, or may be carcinogenic (Dolan et al., 2005; Bercu and Dolan, 2013; Stanard et al., 2015).	Especially potent/toxic compounds, protein nucleic acids

[a] The banding recommendations presented reflect the assumption that an employee will inhale 10 m^3 of air daily during his/her 8-h shift (Derelanko, 2017).
[b] A threshold of 1.5 μg/day is recommended for relatively unstudied compounds which may be mutagenic or carcinogenic (Guideline, 2018).

and the spectrum and severity of clinically observed adverse effects of a specific drug substance, all provide the basis for the hazard assessment. Preclinical data such as QSAR (*in silico* predictive systems) and animal data is also considered in the hazard assessment, and one or more compound characteristic may be responsible for placing a compound in a specific ECB. It is generally prudent to assign compounds to more protective bands earlier in their development, and as new data emerges, subsequently adjust their occupational exposure limits/bands to less restrictive bands and corresponding handling practices (with the goal being to ensure workers in the early development space are adequately protected).

The banding system is integrated into the organization's engineering controls and thus may be different across organizations. For illustrative purposes, Table 1 presents a typical pharmaceutical compound banding system and is the one employed by Bristol Myers Squibb (BMS). The cutoffs for the bands/categories presented are based on several factors, including approaches based on the threshold of toxicological concern (TTC) (NIOSH, 2019; Dolan et al., 2005; Kroes et al., 2004; Cramer et al., 1978; Gould et al., 2016; Guideline, 2018). While the TTC may not be originally derived for occupational purposes, the principles have been applied successfully in the field of occupational health and safety for the establishment of safe occupational exposure limits (Chebekoue and Krishnan, 2017, 2019; Carthew et al., 2009; Hoersch et al., 2018). TTC limits can be applied using an assumed breathing volume of 10 m^3 and 100% inhalation bioavailability. The banding recommendations included in this manuscript for compounds including small molecules, antibody drug conjugates, oligonucleotides and biologic material made through chemical synthesis, are based on those presented in Table 1. For more information on occupational exposure banding systems and applications including suggested exposure controls and handling practices see the following references (Naumann et al., 1996; Zalk and Nelson, 2008; NIOSH, 2019; Ader et al., 2005; Garrod and Rajan-Sithamparanadarajah, 2003).

2.3. Banding considerations for biologics

Due to the general instability of biologic therapeutics, differences in their manufacturing (generally closed processes to protect sterility) and their potential limited bioavailability (BA) via the inhalation, oral and dermal routes (Gould et al., 2018; Pfister et al., 2014a; Bos and Meinardi, 2000; Krause and Sahin, 2019), it can be argued that a different set of exposure controls can be utilized to protect employees when working with biologics as compared to small molecules. Based on this information as well as extensive industrial hygiene monitoring conducted by BMS showing that airborne concentrations of biologics are most often <1 μg/m^3 (data not shown), a simplified two-band system was developed for biologics for use when there is insufficient information available to calculate an OEL. Therefore, a two-category system for banding mid-to high-molecular weight (MW) biologics made through biological processes (i.e., mammalian cell culture) is implemented at BMS and is presented in Table 2. Essentially, active biologic materials that are made through biological processing (i.e. cell culture), can be categorized into one of two Biologic Control Categories (BCC) (BCC A or BCC B). BCC A or BCC B is assigned based on the hazards and potency of the biologic of concern (See Fig. 1). For potent or toxic therapeutic proteins or other biologic compounds, BCC B exposure controls (and corresponding handling practices) should be utilized. Note that while Table 2 illustrates the banding system that BMS implements for biologics, alternative schemes are also utilized in the pharmaceutical industry which are equally effective in controlling exposures. Additionally, for compounds expected to pose special hazards, a compound-specific risk assessment can be completed to confirm whether additional exposure controls are needed (e.g. BCC B controls with additional personal protective equipment). Also, note that once a sufficient data package is available to establish an OEL (also referred to as a health-based exposure limit [HBEL] or an exposure guideline [EG]), the BCC is of limited applicability.

Table 2
Example of a biologic-specific banding system.

Biologic Control Category (BCC)	Range (μg/m^3)	Relevant Compounds	Examples
A	≥1	Biologics with low to moderate toxicity/potency	Mid- to high- MW biological compounds, therapeutic proteins, PEGylated proteins, antibodies, adnectins
B	<1	Especially toxic/ potent biologics	Potent proteins, bispecific antibodies or other large molecule biologics as determined by a case-by-case assessment

2.4. Banding decision tree

In order to assist in the selection of the appropriate ECB or BCC for pharmaceutical modalities discussed in subsequent sections, a decision tree was generated as shown in Fig. 1. The primary consideration for band selection is pharmacological potency *in vivo*, and details regarding derivation of the pharmacological potency levels which can differentiate between bands, bioavailability considerations, and additional toxicities which may warrant an additional safety factor are described in more detail within this article (see Sections 3.1.7 and 3.4.7). This decision tree focuses specifically on ECB 4, 5, and 5 special case (for small molecules) since early in drug development when the banding approach is most applicable, limited data are available such that less restrictive bands would not be considered, and active pharmaceutical ingredients (APIs) would generally default to one of these three bands. It should be noted that this decision tree, and the doses included therein, should be considered as a rough guide for initial band selection. Ultimate selection of the band should come from a qualified occupational toxicologist, and rely on the consideration of a number of additional criteria as described in this article, including the innate hazards of the therapeutic as well as its pharmacokinetic and pharmacodynamic profiles among others.

3. Occupational exposure control banding considerations for pharmaceutical modalities

3.1. Small molecules

3.1.1. Background

Small molecule drugs (<900 Da [Da]) are generally designed to freely enter cells (Dougherty and Pucci, 2011). Once inside a cell, small molecule drugs can interact with proteins, receptors and deoxyribonucleic acid (DNA). This is different from drugs that have a large MW, such as monoclonal antibodies, which are not able to penetrate cells very easily even once they are systemically bioavailable. While there are exceptions, generally oral bioavailability significantly decreases when the molecular size exceeds 900 Da.

3.1.2. How they work

Small molecules exert pharmacologic effects through various mechanisms of action, including but not limited to: 1) agonism/antagonism of specific receptors (e.g. tamoxifen), 2) enzyme inhibition (e.g. apixaban), 3) hormonal interaction (e.g. levonorgestrel), 4) alkylation (e.g. lomustine), and 5) inhibition of transporters (e.g. dapagliflozin). Their small size allows for the possibility of rapid diffusion across cell membranes so that they can reach intracellular sites of action (Dougherty and Pucci, 2011; Veber et al., 2002).

Approximately 20% of all small molecule drugs approved during the period of 2000–2008 were prodrugs (Huttunen et al., 2011) and they

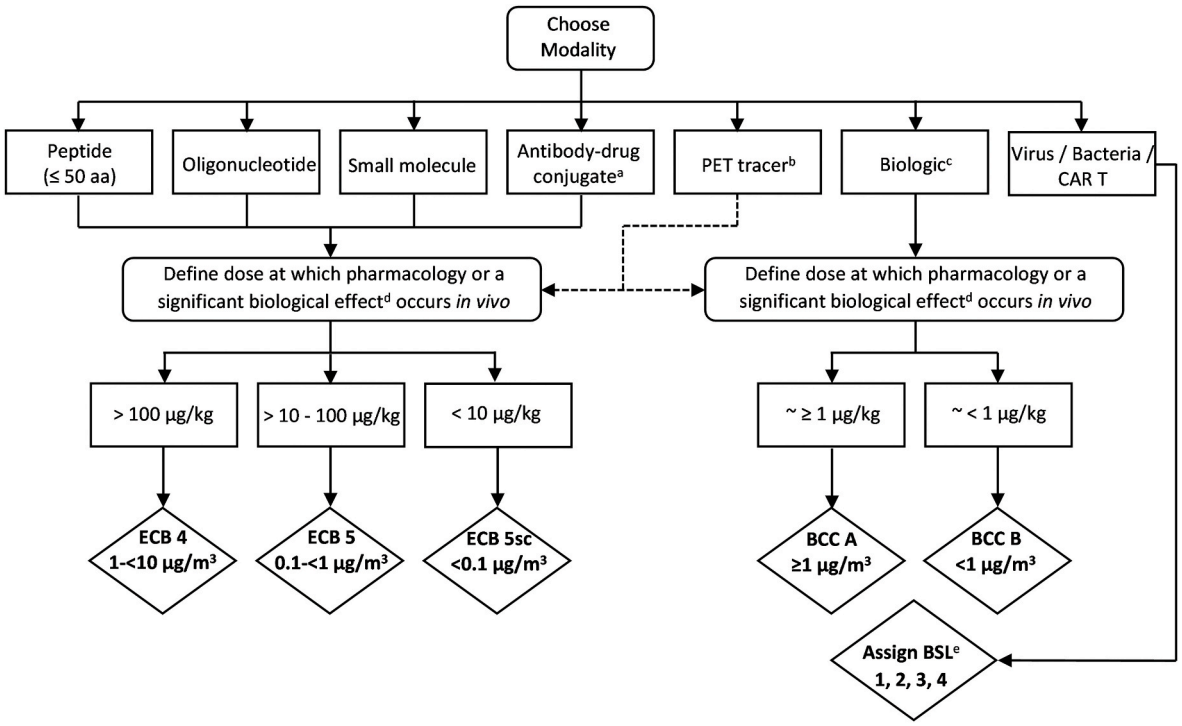

Fig. 1. Occupational Exposure Control Banding Decision Tree for Therapeutic Modalities. Use of this decision tree, and the potencies included herein, should be considered as a rough guide for initial band selection. Ultimate selection of the band should come from a qualified occupational toxicologist, and rely on the consideration of a number of additional criteria such as the innate hazard of the therapeutic, its pharmacokinetics, and pharmacodynamics, among others. For example, an additional safety factor may need to be applied for compounds which are mutagenic or teratogenic, resulting in a more restrictive band.
Footnotes: [a] ADC banding is generally driven by the warhead potency; [b] Follow guidance for radiolabeled compounds, banding is based on the API; [c] Biologic materials made through biological processes (i.e. cell culture); [d] This biologically significant effect should also be clinically relevant; [e] Note that for live viruses, enhanced control measures may be required. Abbreviations: aa = amino acids; sc = special case.

remain a significant portion of drugs being developed (Rautio et al., 2017). Prodrugs are inactive derivatives of active drug molecules that must undergo an enzymatic and/or chemical transformation *in vivo* to release/become the active drug, which can then elicit its desired pharmacological effect in the body (Huttunen et al., 2011).

3.1.3. Marketed drugs

Small molecules make up the majority of marketed pharmaceuticals. Examples of small molecule pharmaceutical drugs include many cardiovascular drugs (e.g. Eliquis® or Apixaban), antivirals (e.g. Daclatasvir or Daklinza®), and diabetes therapeutics (e.g. Farxiga® or Dapagliflozin), to name a few. One example of a prodrug is Vyvanse® (a form of amphetamine used to treat attention-deficit/hyperactivity disorder) which is designed to have less abuse potential than other amphetamines due to the slower release of the active drug following bioconversion in the intestine/liver. Another example of a prodrug is omeprazole (a proton pump inhibitor used to treat acid reflux and ulcers) which is bioactivated site-selectively in the acidic conditions of the stomach.

3.1.4. ADME

The absorption of a small molecule drug is highly variable and dependent on multiple factors including its hydrophobicity/hydrophilicity, size, molecular charge/ionization state, and plasma/protein binding potential. Small molecule drugs are generally administered orally and are designed to have high oral BA, which can give them an ease of use advantage over high MW drugs that require parenteral administration. Small molecule pharmaceuticals are designed to be stable alone and/or in formulation enabling a long shelf-life and the ability to reach cellular targets intact with consistent pharmacological potency (Chen et al., 2018). In most cases, prodrugs are simple chemical derivatives that are only one or two chemical or enzymatic steps away from the active parent drug. Prodrugs are typically designed to improve the pharmacokinetic (PK) profile of the active drug and can also facilitate the intracellular localization of drugs. The liver is generally assumed to be the major site of first-pass metabolism of a small molecule drug administered orally.

There are many different routes of excretion including via the urine, bile, sweat, saliva, tears, milk, and stool. The majority of drugs are eliminated via pathways that involve the kidneys and/or the liver. A major characteristic of compounds excreted in urine is that they are polarized (i.e., charged) and water-soluble. Drugs that are lipid soluble are not readily removed by the kidneys and require hepatic metabolism (e.g. phase I and phase II biotransformation reactions) to increase their water solubility for possible urinary excretion (Kapusta et al., 2007). Drugs with a MW exceeding 300 Da and with polar and lipophilic groups are more likely to be excreted in bile (Lu et al., 2019).

3.1.5. Health hazards associated with therapeutic use

Due to their small size, the oral and inhalation BA of small molecules is often quite high (>50%). In general, the hazards associated with small molecule drugs are due to their pharmacological effects or exaggerated pharmacology. Hazards can also be due to off-target effects.

In general, the hazards of prodrugs are the same as for small molecules. Prodrugs can be metabolized into more active or less active forms, which can contribute to their pharmacology and/or toxicity.

3.1.6. Occupational hazard and exposure considerations

Small molecules can elicit effects via the oral, dermal, inhalation and systemic routes (in addition to others) therefore exposure via each of these occupational exposure routes is of concern. Regarding inhalation exposure, it is important to consider the molecule's potential to exert

direct effects on the lung (e.g. target receptor present in the lung, pulmonary vasodilator) as well as the compound's systemic BA via the inhalation route. In the absence of inhalation BA data, it is acceptable to conservatively assume 100% of the inhaled dose reaches the systemic circulation. There is also the potential for dermal absorption for this class of compounds and therefore the potential for dermal toxicity due to dermal absorption and subsequent systemic exposure.

3.1.7. Occupational exposure banding guidance recommendation

When assigning a small molecule to an ECB (Fig. 1), the goal is to ensure that employees are adequately protected throughout their tenure working with the compound of concern. Since the data to support the calculation of the OEL is not available in the early development space, assumptions need to be made to enable the determination of the appropriate ECB. These assumptions include information and confidence in the dose where biologically significant (and clinically relevant) pharmacology is expected. Adhering to the suggested doses where biologically significant pharmacology is observed in Fig. 1 provides a 100-fold safety factor from the midpoint of the band for a 50 kg individual (bodyweight recommended when establishing permissible daily exposure limits) (Agency, 2014). It is important to note that cytotoxic compounds, mutagens, teratogens and hormones may require a greater safety factor due to their potential for severely toxic effects. It is BMS's practice that the default band for pharmacologically-active, small molecule APIs can be considered to be ECB 4, however this default band should be reconsidered if a molecule is expected to be extremely potent/toxic or based on professional judgment.

Another helpful piece of information when establishing the ECB is the projected (or actual) lowest human therapeutic dose. Compounds which may have a therapeutic dose of <1 mg/day may need to be placed into ECB 5 or 5 special case in order to allow for an acceptable margin of safety, in this instance defined as the exposure margin between the therapeutic dose and the midpoint of the occupational exposure band. Information on the PK of the compound such as half-life and oral BA, along with pharmacodynamics (PD), should also be considered if available. For example, a compound with a long half-life (on the order of days) may bioaccumulate, resulting in a lower acceptable occupational exposure than for a compound with a half-life of hours. For compounds that are prodrugs, the ECB should be consistent with that of the more active form, taking into account the rate of formation of the active and the route of exposure.

3.1.8. Establishing default bands

In the situation where very limited data is available, the API can be assigned to a default band, based on the *in vitro/in vivo* potency, knowledge and/or experience with the therapeutic target and the projected human efficacious dose (if available). As mentioned previously, the default band employed by BMS for pharmacologically-active APIs is ECB 4, however this default band should be reconsidered if a molecule is exquisitely potent or toxic or based on professional judgment resulting from knowledge or experience with the therapeutic target and modality. For example, some modalities are known to have potent toxicity (e.g. ADCs) and therefore can be assigned to a default ECB based on prior experience or information on pharmacologically, toxicologically or structurally similar compounds.

3.2. Oligonucleotides

3.2.1. Background

Oligonucleotides (ONs) are a novel class of therapeutic agents comprised of the nucleotides adenine, guanine, cytosine, thymine, and uracil. ONs are usually made up of 13–25 nucleotides and are designed to hybridize specifically to DNA or RNA sequences. ONs include antisense oligonucleotides (ASO), DNA duplexes, Aptamers, Spiegelmers, and RNA interference compounds (RNAi) such as small interfering RNA (siRNAs) and microRNAs (miRNAs). ONs can be 'locked' (LNA) or 'unlocked' (UNA – unlocked nucleic acid) with LNAs generally having higher stability resulting in a longer half-life and stronger base-pairing potential than their unlocked counterparts. A typical ON is a short chain DNA or RNA molecule, with a MW > 7000 Da, manufactured by an isolated/enclosed process such as solid phase synthesis followed by preparative chromatographic purification and downstream processing. This biosynthetic process is closer to a chemical process than a biological process.

3.2.2. How they work

ONs are currently being investigated for the treatment of a variety of diseases, and are primarily being administered by parenteral injection. ON drugs target mRNA and are generally synthesized to match a specific nucleotide sequence of interest. Pharmacology is dependent on Watson-Crick base pairing between the drug and an mRNA target molecule, a scenario that provides for both high affinity and exquisite specificity. ONs such as RNAi compounds are important tools for therapeutic use because of the roles they play in controlling gene expression. ONs can alter gene expression through a variety of mechanisms by targeting mRNA for degradation by cellular RNase H activation or blocking ribosome initiation of protein translation (Templin et al., 2000).

3.2.3. Marketed drugs

Though there are many clinical trials ongoing (>100 ONs are in clinical trials), there are only a few ON-based drugs approved to date, which include Vitravene® (no longer marketed) and Macugen® (Stein and Castanotto, 2017).

3.2.4. ADME

Once in the systemic circulation, ONs are generally taken up endocytically and distributed to the lysosomes or target mRNA. ONs cleared from the circulation are taken up by the liver, kidneys, spleen, and bone marrow. In a study in which rats received an ON dosed as a single intratracheal (i.t.) instillation, ONs rapidly left the lung via absorption into the systemic circulation and were renally excreted within minutes (Moschos et al., 2011).

3.2.5. Health hazards as a class/modality associated with therapeutic use

Adverse effects associated with an ON are generally related to the sequence's ability to interfere with normal cellular function. Health hazards associated with ONs include target-mediated effects, effects resulting from the binding of the ON to off-target DNA/RNA, and effects due to tissue accumulation (liver, kidney and lung [inhalation exposure]).

Oligonucleotides are generally not associated with genetic toxicity, developmental or fertility effects and have been well tolerated in the clinic. The primary effect of ON administration in rodents appears to be a result of pro-inflammatory effects. Additionally, preclinical studies with ONs have demonstrated histopathologic alterations in the liver and kidneys, which were dependent upon dose level, dosing frequency, and duration of treatment (Alton et al., 2012). Effects on tissues are generally related to deposition and accumulation. The most common effect in the clinic is transient, blood-level-dependent effects stemming from interaction with plasma proteins. Theoretical causes for concern with ONs documented in the literature include the potential incorporation of degradation products of phosphorothioate nucleotides into newly synthesized DNA, as well as the binding of ONs to DNA resulting in triplex formation that could ultimately induce site-specific mutations (Vasquez et al., 2000). While a genotoxicity hazard due to DNA incorporation is unlikely based on available data, it has been recommended that the potential for triplex formation should be assessed if appropriate (Berman et al., 2016).

3.2.6. Occupational hazard and exposure considerations

In the workplace, potential routes of exposure to ONs include inhalation, ingestion (via mucocilliary transport from the lung, hand to

mouth contact, etc.) and dermal contact. Overall, the inhalation BA is expected to be low (Guimond et al., 2008), oral BA is generally unknown and dermal BA will depend on such properties as the MW of the ON.

Regarding occupational exposures to ONs, the primary concern is immunogenicity due to their foreign nucleic acid structure. Based on a favorable PK profile, inhalation delivery is a therapeutic option for ONs and pharmacologically relevant doses for the treatment of localized lung diseases will likely be in the range of 1 mg/kg or less (Templin et al., 2000). Regarding inhalation exposure, adverse effects associated with inhaled ONs such as lung inflammation are: 1) typically dose related, 2) primarily occur at high toxicological doses and 3) have been observed to be reversible upon termination of exposure, suggesting regression of lung inflammation in humans after exposure is terminated (Alton et al., 2012). After inhalation exposure to ONs, reversible lung inflammation has been observed in preclinical studies; however, no toxicity or increased lung inflammation has been reported in patients or healthy individuals (Alton et al., 2012). A pro-inflammatory response observed in studies in higher species such as primates is expected to be of minimal consequence since the mixed monocellular infiltrate characteristic of the response in rodents is absent even after long-term exposure in monkeys. However, the effect of prolonged inhalation exposure to ONs remains unknown as inhaled concentrations have been low and clinical trials have been short in duration.

It is important to note that each ON may have different intrinsic toxicological and PK properties following typical occupational routes of exposure. Therefore, as with small molecules, the specific chemistries of ONs warrant individual risk assessments. LNAs are expected to be more of a concern than naturally occurring DNA/RNA in the workplace.

3.2.7. Occupational exposure banding guidance

Despite their complexity in formulations and large molecular sizes, ONs are considered more similar to small molecules than biologics in that they are manufactured by chemical synthesis processes and as such, are generally expected to follow the small molecule quality guidelines issued by regulatory agencies and the ICH. ONs can be evaluated in a similar manner to small molecules, and assigned to an ECB according to the system outlined in Fig. 1. The recommended default ECB for ONs with insufficient data is similar to that recommended for small molecules: ECB 4 (1 - <10 μg/m^3; <100 μg/day). ONs which are not expected to be highly toxic or carcinogenic can be assigned to ECB 4 (1 - <10 μg/m^3; <100 μg/day). ONs which may be highly toxic, mutagenic or carcinogenic can be assigned to ECB 5 (0.1 - <1 μg/m^3; <10 μg/day).

3.3. Peptides

3.3.1. Background

Peptides are short chains of amino acid monomers linked by amide bonds, the covalent chemical bonds formed when the carboxyl group of one amino acid reacts with the amino group of another. Peptide therapeutics are distinguished from proteins on the basis of size. Generally, a peptide is comprised of approximately 50 amino acids or less (Baldo, 2015).

3.3.2. How they work

Naturally occurring peptides function in crucial physiological roles such as hormones, neurotransmitters, growth factors, ion channel ligands, or anti-infectives (Fosgerau and Hoffmann, 2015). Peptides as therapeutics are recognized for being highly selective and efficacious as well as relatively safe and well tolerated. They also are generally associated with lower production complexity compared with protein therapeutics and small molecules. Current development efforts involve peptide targets with emerging peptide technologies inclusive of multifunctional and cell penetrating peptides, as well as peptide drug conjugates.

3.3.3. Marketed drugs

Approximately 140 peptide drugs were in clinical trials in 2015 with >500 in preclinical development (Fosgerau and Hoffmann, 2015). Examples of peptide-based medicines include Lupron™ for the treatment of prostate cancer and Byetta™ (exenatide) for Type 2 Diabetes. With regards to route of administration, most peptide therapeutics are injectables (e.g. administered subcutaneously or intravenously) (Fosgerau and Hoffmann, 2015).

3.3.4. ADME

Peptides are cleared by the same catabolic pathways used to eliminate endogenous and dietary proteins, and are generally regarded as having a predictable metabolism (Taft et al., 2009). They tend to be chemically and physically unstable in the general environment, are prone to hydrolysis and oxidation, have a tendency for aggregation, exhibit a relatively short circulating plasma half-life and fast elimination, and have low membrane permeability (Fosgerau and Hoffmann, 2015). Several drug delivery strategies employ binding the peptide of interest to the circulating protein albumin as a means of obtaining an extended half-life, leading to less frequent dosing, in some cases only once weekly (Fosgerau and Hoffmann, 2015).

3.3.5. Health hazards as a class/modality associated with therapeutic use

Inhalation of therapeutic peptides has been examined in the clinic and in preclinical studies; however, in these studies the therapeutic target(s) was present in the lung (Hartmann et al., 2015; Fellner et al., 2016; Kuehl et al., 2016; Onoue et al., 2011; Walker et al., 2017). Inhalation studies with peptides have shown that they have the potential to produce local immunogenicity and irritation upon chronic exposure (Fellner et al., 2016). Given that therapeutic doses generally need to be administered with a delivery device to ensure sufficient lung exposure, occupationally relevant airborne exposures to therapeutic peptides are expected to be lower than the levels which would cause adverse effects in the lung. The potential for direct lung effects (resulting from the therapeutic target being present in the lung), however, would need to be considered. For peptides where there is no target in the lung, the inhalation route would be less of a concern, although inhalation BA would still need to be considered. An evaluation of inhalation studies with peptides conducted by Pfister et al. (2014) reported BAs of up to 100%, with most being <50% (Pfister et al., 2014a).

3.3.6. Occupational hazard and exposure considerations

Peptides are generally unstable in the environment (e.g. degrade upon prolonged exposure to light, temperature-sensitive), therefore any pharmacological activity may be lost over time should the material be present on a work surface (Krause and Sahin, 2019). Although there are a few marketed oral peptides, in general peptides are not orally bioavailable due to their instability in the GI tract (Fosgerau and Hoffmann, 2015). Dermal exposure would also be of limited concern due to the size of these compounds, the fact that they are naturally occurring proteins and their relative instability under environmental conditions. Exposure via inhalation is a concern, especially when there are potential targets present in the lung (e.g. compounds that target glucocorticoid receptors). Additionally, enzyme proteins have been reported to cause occupational allergies such as asthma (Basketter et al., 2015). Needle sticks and sharps exposures are also a concern as there is a potential for immunogenicity upon systemic exposure (Fosgerau and Hoffmann, 2015).

3.3.7. Occupational exposure banding guidance recommendation

Based on the chemical synthesis used, small size and higher BA of these compounds compared with large MW biologics, peptides can be banded according to the small-molecule ECB system (See Fig. 1). Even if made via a biologic process, their small size precludes them from the BCC system. Similar to small molecules, peptides can be placed in ECB 4 as a default band. A more conservative ECB can be selected if the

compound is an extremely potent peptide (i.e. Calcitonin), if it can cause direct lung effects or exhibit pharmacology at occupationally relevant exposures and/or if the compound is a respiratory sensitizer. In the case of enzyme proteins, suggested industry exposure and handling guidelines are presented in Basketter et al., 2015 (Basketter et al., 2015).

3.4. Biologics

3.4.1. Background

Biologics are considered therapeutic proteins, antibodies, enzymes, adnectins or other active biologic materials that are made through biological processing (i.e. cell culture).

Monoclonal antibodies: Monoclonal antibodies are typically large molecules which have a MW > 140 kDa and are designed to target specific proteins.

Bispecific antibodies: Bispecific antibodies (bsAbs) are emerging as the next generation of antibodies. Bispecific antibodies generally have a MW ranging from 50 to 60 kDa, and have the potential to improve clinical efficacy as well as safety by targeting two distinct immunoregulatory pathways (Dahlen et al., 2018; Brinkmann and Kontermann, 2017).

Probodies: Probodies are similar to prodrugs but are antibodies engineered to remain inert until activated proteolytically in diseased tissue. In principle, any therapeutic antibody can be converted into probody form. There are two types of probodies, conventional IgG-based probodies and probody-drug conjugates (Polu and Lowman, 2014).

Fusion proteins: Fusion proteins generally consist of a peptide (or other short-lived effector domain) coupled to a 'carrier', which is usually a protein or peptide that contributes to the functional properties of the resultant fusion protein. As peptides have a short half-life owing to proteolytic degradation and are usually rapidly cleared (within minutes) via the kidneys, the peptide can be linked to a protein/fusion partner to enable a more stable molecule with an extended half-life. The crystallizable Fc region of human IgG1 antibody is commonly utilized as a fusion partner for the effector molecule(s) because it extends the fusion protein half-life by recycling via the salvage neonatal Fc receptor (FcRn) receptor, and protects the molecule from lysosomal degradation. The linked effector peptide may have widely varying properties contributing to recognition, binding, and toxicity, while its fused partner may aid in stability and targeting of the chimeric polypeptide (Baldo, 2015).

3.4.2. How they work

Monoclonal antibodies: Antibodies, or immunoglobulins (Igs), are large Y-shaped molecules with Fab (fragment, antigen binding) regions and an Fc (fragment crystallizable) region. Fab regions consist of two variable domains that are designed to recognize and bind to specific antigens. Binding triggers the endocytotic internalization of the mAb and subsequent lysosomal degradation (Ryman and Meibohm, 2017). The Fc region interacts with cell surface receptors, and allows the mAb to activate the immune system (Kennedy et al., 2018). Antibody therapeutics can have activity via antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). In ADCC mediated effector activity, the Fc portion of the mAb binds to an FccR on an effector cell, such as a monocyte, macrophage, or natural killer cell, and the Fab domains bind to cell surface receptors on the target cell. This leads to the destruction of the target cell via phagocytosis by the immune cell or release of cytokines leading to cell death (Ryman and Meibohm, 2017). Monoclonal antibodies are potent and highly selective and they can be agonists, antagonists or neutralizing.

Bispecific antibodies: Bispecific antibodies can target two antigens at once. Companies are developing bispecific antibodies with the objective of creating drugs which encompass the function of two monospecific drugs or which have properties that cannot be achieved with a mixture of monospecific compounds. However, the development of bsAbs is considerably more challenging than development of conventional mAbs.

Based on the types of biological targets and modes of action, bispecific immunotherapies can be divided into three main categories:

(1) T-cell redirectors: Cytotoxic effector cell redirector bsAbs target a tumor-associated antigen (e.g. CD19, CD20, epithelial cell adhesion molecule [EpCAM], B-cell maturation antigen [BCMA]) and the T-cell receptor/CD3 complex, which activates cytotoxic T lymphocytes, thereby redirecting T-cell cytotoxicity to malignant cells.
(2) Tumor-targeted immunomodulators: These bispecific immunotherapies bind to a tumor-associated antigen and an immunomodulating receptor, such as CD40. Such compounds are usually designed to be inactive until binding the tumor antigen, thereby localizing immune stimulation to the tumor environment, while minimizing immune activation elsewhere. This is expected to induce powerful activation of tumor-specific T cells with reduced risk of immune-related adverse events.
(3) Tumor-targeted dual immunomodulators: Bispecific compounds that bind two distinct immunomodulating targets, often combining targeting of PD-1 or PD-L1 with that of lymphocyte-activation gene 3 (LAG-3) or T-cell immunoglobulin and mucin-domain containing-3 (TIM-3). The rationale is to induce superior tumor immunity compared to monospecific antibodies to the same targets (Dahlen et al., 2018).

Probodies: Probodies leverage the upregulation of protease activity in diseased tissue (e.g. cancer, inflammatory diseases) to achieve disease-tissue-specific therapeutic activity. The probody remains intact and is blocked from binding to the antigen target, however, once the linker peptide is cleaved by proteases that are selectively activated in the diseased-tissue, the masking peptide is released, allowing the active antibody to bind to its target, resulting in tissue-specific activity (Polu and Lowman, 2014). Preclinical studies have demonstrated that a therapeutic antibody with known on-target toxicity can be reengineered as a probody retaining potent *in vivo* efficacy, but with greatly reduced side effects (Desnoyers et al., 2013).

Fusion proteins: Fusion proteins have been used in the biopharmaceutical industry for over 25 years to improve the PK properties of otherwise short half-life biologics (Strohl, 2015). Fusion proteins offer the potential to target a therapy to the location of disease by combining a targeting component such as a mAb with a therapeutic peptide or protein such as a cytokine. This avoids short half-lives, dose-limiting toxicities, and sub-optimal localization of the therapy, which may be encountered if the unbound therapeutic peptide or protein was systemically administered. Many approved fusion proteins work as agonists (e.g. alefacept) or antagonists (e.g. belatacept, etanercept) of receptor function, or by a direct targeted cytotoxic killing effect (e.g. denileukin-diftitox). Antibody-cytokine fusion proteins, often referred to as immunocytokines, are being utilized to employ the tumor-targeting ability of mAbs to guide the cytokines specifically to tumor sites where they can stimulate anti-tumor immune responses while avoiding dose-limiting systemic toxicity (Young et al., 2014; Hutmacher and Neri, 2019).

3.4.3. Marketed drugs

Monoclonal antibodies: Currently, most mAbs developed are humanized or fully human. The use of mAbs has expanded exponentially during the last decade and currently covers several therapeutic areas, such as oncology, respiratory diseases, hematology, immunology, cardiovascular diseases, and inflammatory diseases (Singh et al., 2018). In 1992, the FDA approved the first therapeutic mAb Muromonab-CD3 (trade name Orthoclone OKT3) to reduce acute rejection in patients with organ transplants (Cai, 2018). As of May 10, 2018, the FDA had approved 80 therapeutic mAbs with indications includinging immune-mediated disorders (e.g. brodalumab, dupilumab) and cancer indications (e.g. avelumab, ocrelizumab) (Cai, 2018; Kaplon and

Reichert, 2018).

Cancer immunotherapies have been established as a highly effective therapeutic option. Ipilimumab was a first-in-class T-cell potentiator that works by blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4), a critical protein receptor that downregulates the immune system (Tarhini et al., 2010). Other approved mAbs include programmed death 1 cell surface receptor (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors such as nivolumab which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response (Singh et al., 2018).

Bispecific antibodies: T-cell redirecting therapies are the most established class of bsAbs, with two approved products, blinatumomab and catumaxomab (later withdrawn), and several others in clinical and preclinical development (Dahlen et al., 2018). In July 2017, the FDA approved blinatumomab (aka Blincyto, CD3XCD19), a bsAb for acute lymphoblastic leukemia (ALL) in adults and children. Blinatumanb targets CD19, a protein on the surface of normal and B-cell malignancies, and the CD3 receptor on the surface of cytotoxic T lymphocytes. Additionally, the first FDA-approved non-oncology bsAb was emicizumab (bsAb recognizing coagulation factor IXa and the substrate factor X) for the treatment of hemophilia A in 2017 (Labrijn et al., 2019; Lenting et al., 2017).

Probodies: Currently a pipeline of probody candidates in oncology are in preclinical development and clinical trials with the potential to reduce side effects and broaden the range of effective doses. However, there is no approved probody for therapeutic use (Autio et al., 2020).

Fusion proteins: More than a dozen fusion proteins have received regulatory approval for human therapy including etanercept, belatacept and denileukin-diftitox (Strohl, 2015). Most approved fusion protein therapies are Fc-fusion proteins, which utilize the Fc fragment of human IgG1 to interact with Fc receptors on immune cells. Importantly, the neonatal Fc receptor (or FcRn) normally functions to transport Igs across cells and to protect circulating Ig from degradation.

Etanercept (Enbrel®) was the first chimeric fusion protein to gain regulatory approval in 1988. Etanercept is a dimeric fusion protein (MW 150 kDa) consisting of a tumor necrosis factor α (TNF-α) receptor ligand-binding region linked to the Fc portion of human IgG1 which acts by binding tumor necrosis factor (TNF) thereby inhibiting the interaction of this cytokine with cell surface TNF receptors and ultimately reducing the ensuing inflammatory response. Etanercept is indicated for the treatment of rheumatoid and other forms of arthritis and is one of the most commercially successful fusion protein therapies (Baldo, 2015).

Belatacept (Nulojix®) is a fusion protein of the Fc fragment of human IgG1 and the extracellular domain of CTLA-4, indicated as prophylaxis against organ rejection in adult patients receiving a kidney transplant. Belatacept blocks CD28-mediated T-cell activation and the production of cytokines by binding CD80/CD86 on antigen presenting cells.

3.4.4. ADME

Due to their large size and potential to be broken down in the GI tract, most "large molecule" biologics (e.g. mAbs, bsAbs, fusion proteins) are primarily administered by intravenous (IV) infusion or injection rather than via the oral route. They are designed to be stable molecules and to have long half-lives typically in the range of days or weeks supporting intermittent administration (Trivedi et al., 2017). Additionally, the conjugation or pegylation of proteins can extend the half-life further (Baldo, 2015). Fusion proteins have been noted to have significantly shorter half-lives then general mAbs (Baldo, 2015).

Notably, large molecules have different PK profiles than conventional small molecule drugs. The PK and serum half-life of bsAbs may or may not be linear depending on the presence of an Fc domain, the absence of which can lead to linear PK. For example, blinatumomab is a recombinant non-glycosylated protein that does not have an Fc domain, thus it does not undergo FcRN-mediated recycling and has a short elimination half-life of roughly 2 h and negligible renal clearance (Trivedi et al., 2017).

Protein therapeutics are cleared via the same catabolic pathways utilized to eliminate endogenous and dietary proteins (Taft et al., 2009). Due to the high binding specificity and affinity of the mAb for its target, target-mediated drug disposition (TMDD) is a major route of elimination for many mAbs with a membrane-standing target, especially at low doses and concentrations. TMDD consists of receptor-mediated endocytotic internalization of the IgG molecule and subsequent lysosomal degradation. The rate of elimination of a protein therapeutic is dependent on the expression of the target receptor, the affinity of the mAb for the receptor, the dose of the mAb, the rate of receptor therapeutic protein internalization, and the rate of catabolism within the target cell. It is important to note that the antibodies cleared primarily by TMDD will have dose-dependent nonlinear elimination. Additionally, the formation of anti-drug antibodies (ADAs) can neutralize mAbs and cause them to be cleared faster (Vande Casteele and Gils, 2015).

The clearance of therapeutic monoclonal antibodies (mAbs) typically does not involve cytochrome P450 (CYP450)-mediated metabolism or interaction with cell membrane transporters (Ferri et al., 2016). Although both the kidney and liver can metabolize proteins by hydrolysis, there is minimal clearance of protein therapeutics via conventional renal and biliary excretion mechanisms (Taft et al., 2009). Unlike small molecules, mAbs are too large to be filtered by the kidneys and are not eliminated in the urine in healthy individuals (Ryman and Meibohm, 2017). Biliary excretion accounts for a very small amount of the elimination of IgG antibodies. Thus, IgG elimination occurs mostly through intracellular catabolism by lysosomal degradation to amino acids after uptake by either pinocytosis, an unspecific fluid phase endocytosis, or by a receptor-mediated endocytosis (Ryman and Meibohm, 2017).

3.4.5. Health hazards as a class/modality associated with therapeutic use

As biologics are specific for their target(s) and are generally administered systemically, they can be especially potent. Bispecific antibodies, for example, can be quite potent, with *in vitro* potency in the low picomolar range and *in vivo* potency at doses <0.1 mg/kg. In an FIH study where catumaxomab was administered IV, fatal acute liver failure and cytokine release-associated systemic toxicity were observed at doses as low as 10 μg (Mau-Sorensen et al., 2015).

Often, mAbs are not tested for their genotoxicity or carcinogenicity since they are not expected to interact directly with DNA or other chromosomal material. Concerns for effects on fertility and developmental toxicity generally depend on the pharmacology of the biologic. For example, compounds which activate the immune system have the potential to cause developmental toxicity, evidenced by the fact that spontaneous abortions have been observed in ePPND monkey studies with immune-modulators, therefore developmental toxicity is a concern for biologics with these modes of action (Brennan et al., 2010). Another example involves biologics which target EGFR, a receptor involved in fetal development, which is likely essential for normal organogenesis, cell proliferation, and cell differentiation in the developing embryo. The mAbs bevacizumab, cetuximab, panitumumab, and trastuzumab bind with the EGFR and inhibit the function of the receptor, resulting in developmental toxicity (Halsen and Kramer, 2011). Additionally, mAbs in the IgG2 subclass are able to cross the placenta (Halsen and Kramer, 2011).

Immunogenicity is a concern with administration of biologic materials. The immunogenic potential of a biologic increases with the proportion of foreign protein, and therefore humanized mAbs have less sensitizing potential than murine mAbs (Halsen and Kramer, 2011). Although Fc fusion proteins are generally safe, adverse events observed with fusion protein therapies include Type I, II, III and IV hypersensitivities such as anaphylaxis, cutaneous manifestations, infusion, and injection site reactions (~20–50% of patients), and cytokine release syndrome (CRS) (Baldo, 2015). The mechanism of action should also be taken into account when determining the health hazards associated with the fusion protein being assessed. Many fusion proteins effect the

immune system, so increased risk of infection, reduced immune system function and autoimmune responses are a concern. For example, the most common adverse effects of etanercept are relatively mild and consist of fever, headache, injection-site reactions, mild allergic reactions, and pruritus (Baldo, 2015). Importantly, some fusion protein-induced skin responses may represent direct targeting events that are not genuine hypersensitivities and are similar to, for example, agents that bind EGFR causing non-immune-mediated adverse cutaneous events (Baldo, 2015). Proteins conjugated with a polyethylene glycol (PEG) carry additional safety concerns around the lack of biodegradability of the PEG component.

It has been shown that FcRn is expressed in both the upper and central airways in non-human primates as well as in humans. After deposition of the aerosolized protein in the lung, transport of the Fc-fusion proteins occurs through binding to FcRn in the epithelial cells followed by transport to the underlying tissue and ultimately into the systemic circulation. The bioavailabilities for Fc-fusion molecules in non-human primates have been in the range of 20–50% when given by inhalation (Dumont et al., 2005). Monomeric fusion proteins are expected to have higher bioavailabilities than dimeric due to their decreased size among other factors (Dumont et al., 2005). For example, the BA of the therapeutic protein erythropoietin-Fc fusion molecule (~112 kDa) in monkeys was ~6% with the dimer and ~35% with the monomer (Dumont et al., 2005). Additionally, many biologics are designed to have long half-lives and may bioaccumulate upon repeated dosing.

3.4.6. Occupational hazard and exposure considerations

As biologics are generally specific for their target(s) and can be quite potent, they should be evaluated on a case-by-case basis. The potential for accumulation due to long half-lives, the pharmacodynamic profile and the potential for developmental toxicity should be considered in the hazard assessment for biologics.

Regarding exposure risks, exposures via the dermal, oral and inhalation routes are generally expected to be low. Compounds >500 Da are not expected to be bioavailable via dermal exposure (Bos and Meinardi, 2000). Low systemic exposure potential is generally expected via the inhalation route of exposure (e.g. BA<1%) in the occupational setting for biologics with a MW > 10 kDa (Gould et al., 2018; Pfister et al., 2014b). Limited studies conducted on the inhalation BA of Fc-fusion proteins, have shown BAs of 20–50%, which is substantially higher than the BA observed with mAbs, emphasizing the importance of considering the binding component when estimating the inhalation BA of fusion proteins (Gould et al., 2018; Dumont et al., 2005; Pfister et al., 2014b). Low BA may not be the case when there are drug targets present in the lung/skin.

Regarding sensitization potential, there are currently no validated *in vitro* or *in vivo* models for respiratory sensitization potential. Available screening tools are generally based on historical data for known respiratory sensitizers; therefore, the structure of the biologic should be examined for potential similarities to known respiratory sensitizers.

Occupational exposures to therapeutic proteins (like other drugs) should be kept to a minimum (de Lemos et al., 2018). While exposure can never be truly proven to be zero, occupational exposure limits, engineering controls, administrative controls, and PPE are necessary to protect employees. Dermal exposure to drugs is never recommended and this remains the recommendation for biologics.

3.4.7. Occupational exposure banding guidance recommendation

The default BCC for mAbs, probodies and fusion proteins which are expected to exhibit pharmacology at doses of ≥1 μg/kg is considered to be BCC A (≥1 μg/m^3), after accounting for the low systemic BA following inhalation (e.g. less than 1%) for compounds with a MW > 10 kDa. For biologics where a pharmacological effect is expected at <1 μg/kg, BCC B is generally appropriate. It is also important to take into consideration the potential for direct lung effects and when the drug target is present in the lung since adverse effects would not be dependent on systemic BA in this case.

Due to the high potency and generally low clinical doses associated with bsAbs, the default BCC for bsAbs is considered to be BCC B (<1 μg/m^3), even after taking into account the low inhalation BA and high MW.

3.5. Antibody-drug conjugates

3.5.1. Background

Antibody drug conjugates (ADCs) are a novel class of therapeutic agents typically developed as treatments for cancer that are characterized by an antibody scaffold covalently modified with a variable number of small-molecule payloads. The payloads are generally highly potent cytotoxic chemicals (known as warheads) and are bound to the antibody scaffold via synthetic linkers. Such immuno-conjugates combine the anti-tumor potency of highly cytotoxic small-molecule drugs (300–1000 Da, with subnanomolar IC_{50} values) with the high selectivity, stability, and favorable pharmacokinetic profile of monoclonal antibodies (Drake and Rabuka, 2017). These drugs are hybrid entities combining both biologic and small-molecule characteristics, where the antibody serves to target the small molecule specifically to the intended cell type.

3.5.2. How they work

ADCs are currently being investigated for the treatment of a variety of cancers. The mechanistic basis for the ADC activity includes its specific binding to the cellular target, triggering ADC cellular internalization by pinocytosis, followed by the intracellular release of the payload (Roberts et al., 2013). Therefore, after administration into the systemic circulation, the antibody fragment guides the complex to the targeted tumor antigen where it becomes internalized into the cancer cell (Hasan et al., 2018). The intracellular release of the payload in its active form results in cell death. The three components of ADCs, namely the antibody, the linker and the cytotoxic drug, have their own inherent characteristics and limitations which influence each other, thus finding the best combination of these components to design an ideal ADC is a complicated task (Hasan et al., 2018). Although this targeted approach appears straightforward, its translation to clinical practice has been problematic with initial attempts failing due to inappropriate linker systems or insufficiently potent cytotoxins, resulting in unfavorable therapeutic indices. Modern ADCs tend to use highly potent cytotoxic molecules, such as derivatives of calicheamicin, maytansine and auristatins (Senter, 2009; Ducry and Stump, 2010). A number of these molecules have demonstrated substantial *in vivo* antitumor activity. To translate the fundamental advantage of ADCs in targeting tumor-selective or tumor-specific antigens in clinical practice, it is essential that linkers be of sufficient stability to minimize systemic exposure to the cytotoxin and the resulting toxicities, while still providing sufficient targeted intracellular release of the cytotoxic agent (Roberts et al., 2013).

3.5.3. Marketed drugs

There are currently four ADCs marketed in the US, although there are over 60 ADCs in clinical trials (Garcia-Alonso et al., 2018). Gemtuzumab ozogamicin (Mylotarg™) was the first marketed ADC, originally approved in 2000 for treatment of CD33-positive acute myeloid leukemia (AML). However, it was withdrawn from the market in 2010 due to treatment-related toxicity concerns. Mylotarg™ was reapproved in 2017 with a lower recommended dose and altered dosing schedule for the treatment of adults with newly diagnosed CD33-positive acute myeloid leukemia (AML) and for patients ages 2 years and older with relapsed or refractory CD33-positive AML. In 2011, brentuximab vedotin (Adcetris©), an anti-CD30 monomethyl auristatin E (MMAE) conjugate gained market approval for the treatment of relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. In 2013, trastuzumab emtansine (Kadcyla©), an anti- HER2 directed ADC conjugated to DM1 (also called mertansine, a potent antimicrotubule agent) was

approved for the treatment of HER2+ metastatic breast cancer. Additionally, in 2017, another ADC was approved by the FDA, which included a cytotoxic agent from the class of calicheamicins. Inotuzumab ozogamicin (Besponsa©), which targets CD22 was approved for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (Garcia-Alonso et al., 2018).

3.5.4. ADME

ADCs are large molecules (~150 kDa) typically administered systemically by intravenous (IV) infusion (Malik et al., 2017). After systemic administration, the distribution of the intact ADC is generally confined to the plasma, interstitial fluid, and lymph (Han and Zhao, 2014). They often possess long plasma residence times because of their dynamic interactions with the FcRn (Garg and Balthasar, 2007) and are therefore administered intermittently, typically once every 1–4 weeks (Malik et al., 2017). In most, but not all cases, ADCs exhibit nonlinear PK and dose-dependent clearance due to saturable target binding and elimination (Levy, 1994). Plasma stability and the extent of deconjugation in circulation can be estimated with direct measurements of the conjugated fraction (Kraynov et al., 2016). The free payload concentrations can be used to evaluate payload dependent toxicity, although this toxicity is difficult to distinguish from toxicity that occurs when the conjugated antibody is taken up into normal tissues (Poon et al., 2013). ADCs are designed to bind membrane-bound target proteins that can facilitate internalization into tumor cells by receptor-mediated endocytosis (Ritchie et al., 2013). Because of the high affinity of the initial binding interaction, ADCs undergo target-mediated drug disposition (TMDD), meaning that the properties of the target influence the PK of the drug (Mager and Jusko, 2001). Target expression, internalization, turnover, accessibility and binding affinity all impact the PK of ADCs. After administration, ADCs distribute to occupy target sites that are present in both normal and diseased tissue.

3.5.5. Health hazards as a class/modality associated with therapeutic use

The health hazards of ADCs may be dissected into the relative parts or building blocks of these hybrid molecules and can also be evaluated for the ADC as a whole. There are the obvious hazards associated with the highly potent cytotoxic payload, hazards associated with the monoclonal antibody scaffold, and hazards associated with the linker molecules, which can then vary depending if the linker is bound with the payload or antibody.

The potent cytotoxic payloads typically utilized in ADCs include DNA double strand breakers such as Calicheamicin (Mylotarg©) or esperamycin; DNA alkylating agents such as duocarmycin, cyclopropabenzidole (CBI), or pyrrolobenzodiazepines (PBD); and inhibitors of tubulin polymerization such as maytansine (T-DM1), auristatin (SGN-35), or tubulysin (Beck et al., 2017). These agents typically induce cell death in rapidly dividing tissues and induce hematologic and GI toxicity. Genotoxicity, and reproductive and developmental toxicities are also associated with exposure to these highly potent cytotoxic drugs, and neurotoxicity is a known adverse effect of the tubulin disruptors (Remesh, 2012). Radio-nucleotides were also historically used as ADC payloads, but have been replaced in modern ADCs by the use of these highly potent cytotoxic drugs (Hasan et al., 2018).

The antibody scaffolds may have potential toxicity resulting from the intended and unintended pharmacological action as well as immunogenic effects associated with exposure to proteins. Proteins are thought to have lower potential to cause harm, and most of these are humanized antibodies with a lower potential for off target immunological events. They are designed to preferentially target cancer cells rather than normal tissues, which can lower the hazard of off target pharmacology.

The linkers are typically small molecules with hazards that may vary and need to be assessed on a case-by-case basis. Linking strategies that take advantage of the properties of endogenous amino acids (such as engineered antibodies or peptides) are unlikely to be toxic on their own, or to significantly contribute to the toxicity of either the antibody or the payload. The toxicity of other types of linkers would need to be evaluated on a case-by-case basis. Potential issues include the possibility of linking to endogenous proteins or other cellular macromolecules, or altered immune responses.

For the ADC as a whole, it is important to note that even though the payload is connected to an antibody, it does not mean that the toxicity to the payload will be reduced. There is a strong possibility that the payload could be released despite not having a (tumor) binding site. Therefore, it is critical to account for the hazards associated with the payload and not to assume the linker to the antibody is systemically stable.

3.5.6. Occupational hazard and exposure considerations

In the workplace, potential routes of exposure to the intact ADC or its respective components include inhalation, ingestion (via mucocilliary transport from the lung, hand to mouth contact, etc.) and dermal contact (depending on MW, etc.). The overlying concern with occupational exposure to these types of molecules is the highly potent and toxic nature of the payload component. A critical attribute of any ADC is the amount of drug loading, or the average ratio of conjugated payload to antibody. This is referred to as the drug-to-antibody ratio (DAR). Since the DAR dictates the amount of payload delivered per internalized antibody, it strongly influences both efficacy and toxicity. In addition, depending on the conjugation and linker technologies used, high-DAR ADCs can have poor biophysical characteristics (e.g., hydrophobicity, aggregation) that reduce efficacy and increase toxicity (Drake and Rabuka, 2017). Another important factor to consider when assessing the toxicity of the ADC and individual components is the relative size of the component molecules. While the payload and linker may have molar masses in the several hundreds of Da, the antibody will typically have a molar mass of around 150,000 Da, though antibody fragments may be significantly smaller. As such, the payload element of the ADC may only constitute less than 0.5% by weight of the total MW; a potentially important fact when safe exposure levels are typically quoted in mass terms. Of course, with smaller antibody fragment utilization, this effect will be reduced and the toxic payload will constitute a greater proportion of the compound mass.

During each step to the manufacturing process, the hazards may change based on the nature of the components being utilized in that step of the manufacturing process. The relatively low toxicity of antibody proteins, and the common processing of such macromolecular materials in enclosed solution or suspension forms, results in a relatively low risk of intolerable exposure by main traditional routes (inhalation, ingestion and skin absorption). In addition, the BA of such large biologically derived macromolecules by traditional exposure routes (ingestion and airborne inhalation) is low due to instability of proteins in the GI tract as well as low inhalation BA of such large molecules from the respiratory tract. The processes used for the manufacture of payload and subsequent conjugation to the antibody scaffold are typical “wet chemistry” covering all normal synthetic chemistry and pharmaceutical processing steps for small molecules, which includes the synthesis of the payload and linker and associated purification and isolation steps including chemical reaction, chromatography distillation, filtration, crystallization, drying and lyophilization, with solvent recovery and emission control. Given the known toxicities of payload materials, activities such as payload manufacture and handling of pure payload material prior to conjugation, and especially any processes involving open handling of such materials, especially in a dry powder form, are considered a high risk of unacceptable exposure. Similarly, ancillary activities such as Quality Control (QC) testing and cleaning, where exposure to the payload as either a trace residue or component of a sample may occur, should also be considered.

Major concerns during synthesis and conjugation will include all activities where manual intervention is required, transfer of materials between processes except in sealed transit routes, and in recovery and storage of the high toxicity material in a form which may present

enhanced emission risks by certain routes; for example as a dry friable solid for airborne transfer, or as a solution in an organic solvent for transdermal transfer. The high toxicity of the payload and of the ADC requires a more rigorous consideration of the routes of exposure than might be typical for small molecule applications where typically only airborne and (occasionally) surface transfer routes are considered. It is important to note that a payload could be released from an ADC despite not having a binding site. Therefore, it is critical to protect directly for the contribution of the payload and not to assume the linker to the antibody is systemically stable. The extreme toxicity of the payload warrants consideration of all routes, with control of hand contamination in particular being a concern as this is a major transfer route into ocular and ingestion routes of exposure. The high toxicity and uncertainty of exposure uptake efficiencies means that other activities that may lead to exposure to trace levels of residues, such as might occur during manual cleaning of contaminated equipment, may be significant, and the potential and mechanisms for equipment and containers to become contaminated on exposed external surfaces should also be assessed.

3.5.7. Occupational exposure banding guidance recommendation

Occupational exposure banding recommendations are based on the inherent hazards associated with exposures to each component of the ADC manufacturing process. Therefore, those components containing the intact or generally active payload, which would include the payload itself and the payload plus the linker, which are all small molecules components, are assigned to ECB 5 special case (<0.1 μg/m^3) due to their highly potent cytotoxic hazards. The intact ADC, while retaining the cytotoxic hazards, is assigned to ECB 5 (0.1 - < 1 μg/m^3) due to its mixed biological/small molecule dilution effect. The intact antibody components are assigned to Biologic Control Category A (≥1 μg/m^3). The linker molecules are typically evaluated on a case-by-case basis, but generally fall within ECB 3 (10 - <100 μg/m^3; <1000 μg/day) or ECB 4 (1 - <10 μg/m^3; <100 μg/day).

3.6. Positron-emission tomography (PET) tracers

3.6.1. Background

Positron-emission tomography (PET) is a nuclear medicine functional imaging technique that is used to observe biochemical processes in the body and for the detection of many diseases. PET imaging tracers enable molecular imaging that relies on derangement of physiological and biochemical processes for the detection of many diseases (Hicks et al., 2006).

3.6.2. How they work

The PET imaging system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide tracer, which is introduced into the body on a biologically active molecule. This tracer can be a small or large molecule that has been labeled with a radioactive element (commonly fluorodeoxyglucose, 11C, 18F, 64Cu, 89Zr) (Hicks et al., 2006).

3.6.3. Marketed drugs

While the first radiopharmaceutical approved by the FDA was sodium Fluoride F-18 in 1972, the majority of PET imaging agents have been approved in the past 10 years (Clarke, 2018). Examples of approved PET agents include Axumin® and 68Ga-DOTATATE, indicated for imaging prostate tumors and neuroendocrine tumors (NETs), respectively.

The PET Tracer Axumin® is indicated for Positron Emission Tomography—Computed Tomography (PET/CT) imaging in men with suspected prostate cancer for men with elevated blood prostate specific antigen (PSA) levels following prior treatment. Axumin® contains fluciclovine, a fluorine 18 (F 18) labeled synthetic amino acid. Since amino acids are key nutrients for tumor growth, fluciclovine is readily incorporated into dividing tumor cells. It is administered as an injection, is transported rapidly into cells by amino acid transporters (uptake time 3–5 min) (Clarke, 2018).

NETs have receptors for somatostatin, a hormone that regulates the endocrine system. 68Ga-Dotatate (AAA's NETSPOT®) is a positron-emitting analogue of somatostatin, which works by binding to somatostatin receptors enabling imaging of NETs. 68Ga-DOTATATE is comprised of DOTA-TATE, an amino acid peptide, with a covalently bonded DOTA bifunctional chelator, bound to radionuclide gallium-68 (Clarke, 2018).

3.6.4. ADME

Distribution of a PET agent is going to depend on its receptor specificity and intended area(s) of localization. Based on clinical studies, the organs with the highest radiation from 18F radiotracers are the urinary bladder and gallbladder followed by the kidney, liver, pancreas and lungs (Zanotti-Fregonara et al., 2013). The elimination half-lives are generally in the order of hours, for example with those of Axumin® and 68Ga-DOTATATE being 110 min and 68 min, respectively (Clarke, 2018).

3.6.5. Health hazards as a class/modality associated with therapeutic use

The pairing of a radioactive element with a targeted drug/compound results in a dual hazard, one from the toxicity of the compound or drug substance and one from the radioactive effects. Non-ionizing radiation is essential to life, but excessive exposures will cause tissue damage. All forms of ionizing radiation have sufficient energy to ionize atoms that may destabilize molecules within cells and lead to tissue damage (Occupational Safety, 2020). The hazards attributable to the small molecule or target-oriented compound are aligned with those described herein under the appropriate modality.

3.6.6. Occupational hazard and exposure considerations

With regards to the occupational hazard of radiation exposure, the guiding principle of radiation safety is that exposure be controlled to "as low as reasonably achievable" ("ALARA") (Control CfRadiatio, 2015). Radioactive hazards are addressed using the techniques detailed by several organizations (Occupational Safety, 2020; EPA, 2020); and are focused on limiting the time spent near a radiation source, maximizing the distance from the radiation source and shielding from a radiation source (Directive C, 2013).

3.6.7. Occupational exposure banding guidance recommendation

The compounds and/or drug substances which are "attached" to the tracer should be addressed as if there were no radioactive tracers present and would maintain their ECB or BCC that existed prior to the radiolabeling.

3.7. Chimeric antigen receptor (CAR) T cell therapies

3.7.1. Background

Adoptive T-cell therapy (ATC) refers to the use of *ex vivo* culture and cellular engineering to modify a patient's own lymphocytes in order to elicit anti-viral, anti-inflammatory, or anti-tumor effects. There are currently three forms of ACT being developed for cancer therapy specifically, including tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR) T cells, and chimeric antigen receptor (CAR) T cells (June et al., 2018). CAR T-cell therapy involves the isolation of a patient's autologous T cells via leukapheresis, genetic modification of said cells *ex vivo* using viral and non-viral transfection methods (e.g. viral transduction, DNA-based transposons, CRISPR/Cas9), modified cell expansion in culture, and finally, re-infusion of the CAR T-cells back into the patient. This genetic modification involves transgenic expression of a CAR for a cell surface receptor(s) or antibodies (e.g. CD19, CD22, BCMA) specific to cancer targets, essentially re-directing a patient's T cells to specifically target and destroy tumor cells (Miliotou and Papadopoulou, 2018).

3.7.2. How they work

As opposed to normal TCRs, CARs are able to recognize a number of different elements expressed on the surface of tumor cells including unprocessed antigens, carbohydrates, and glycolipids, all without requiring antigen presentation by the major histocompatibility complex (MHC) (Schmidt-Wolf et al., 1991). The fact that CAR recognition is independent from MHC class I and II restriction means that CAR T-cells of both $CD8^+$ and $CD4^+$ subsets can be redirected to recognize the tumor cell directly, thereby offering a fundamental antitumor advantage since loss of MHC-associated antigen presentation by tumor cells is a primary mechanism of cancer immunoevasion (Garrido et al., 2016). CAR-mediated tumor elimination by redirected $CD8^+$ and $CD4^+$ T-cells occurs primarily via cytolysis mediated by either perforin and granzyme exocytosis, or death receptor signaling through Fas/Fas-ligand or tumor necrosis factor (TNF)/TNF-receptor (Miliotou and Papadopoulou, 2018; Chmielewski et al., 2013).

3.7.3. Marketed drugs

CAR T cells are the first form of gene transfer therapy to gain commercial approval by the U.S. FDA, and there now more than 250 clinical trials evaluating the effectiveness of this therapy (June et al., 2018). The majority are directed against hematological malignancies, although there are ongoing efforts to apply this therapeutic approach more broadly to solid tumors such as glioblastoma (Brown et al., 2015) and head and neck cancer (van Schalkwyk et al., 2013). To date, there are two FDA-approved CD19-directed autologous CAR T-cell therapies: (1) tisagenlecleucel (Kymriah™), approved for adults with relapsed or refractory diffuse large B-cell lymphoma, and you adult patients up to age 25 with relapsed or refractory acute lymphoblastic leukemia, and (2) axicabtagene ciloleucel (Yescarta™), approved for various types of B-cell lymphoma that have either not responded to, or have relapsed following two or more lines of systemic therapy. Given the high cost of autologous CAR T-cell therapy, there are efforts to develop allogenic CAR-T-cells sourced from healthy donors and cryopreserved for future use as an "off-the-shelf" product. Cellectis, for example, is developing allogenic CAR T-cell therapies targeting a number of protein markers including CD19, CD22, CD38 and CS1 (Yip and Webster, 2018).

3.7.4. ADME

The conventional ADME criteria that apply to modalities such as small molecules and biologics, are not necessarily applicable to CAR T-cells. Because a CAR transgene is permanently integrated in the T-cell genome, the equivalence to ADME for this modality is cell infusion, trafficking, proliferation, persistence, and apoptosis (Mueller et al., 2017; Wang, 2017). In consideration of approved CAR T-cell therapies specifically, both Kymriah™ and Yescarta™ exhibited an initial rapid expansion immediately following infusion (peak levels occurred within the first 7–14 days for Yescarta™), followed by a decline to near baseline levels (by 3 months for Yescarta™). For Kymriah™, the transgene was present in the blood and bone marrow and was measurable beyond 2 years, with high distribution to bone marrow (44%, 67%, and 69% of that present in the blood at Day 28, Month 3, and Month 6, respectively) (Novartis, 2017; Food and Administration D, 2018).

3.7.5. Health hazards as a class/modality associated with therapeutic use

Toxicities associated with CAR T-cell therapy are summarized in Table 3. The most common adverse effect following CAR T-cell infusion is immune activation known as CRS, similar to what has been observed following infusion of therapeutic mAbs, bispecific antibodies, and systemically administered IL-2 (Bonifant et al., 2016). CRS is the result of elevated inflammatory cytokines (interferon gamma, granulocyte macrophage colony-stimulating factor, IL-10, IL-6) being released once the CAR T-cell engages surrogate antigens. Other innate immune system cells also become activated and subsequently release additional soluble mediators. CRS presents clinically as high fever, malaise, fatigue, myalgia, nausea, anorexia, tachycardia/hypotension, capillary leak, cardiac dysfunction, renal impairment, hepatic failure, and disseminated intravascular coagulation appearing 1–2 h after the first infusion (Lee et al., 2014). The incidence rate of CRS in patients receiving CD19 CAR T-cell therapy ranged from 54 to 91%, including severe CRS in 8.3–43% (Hay et al., 2017).

Table 3
Adverse effects associated with CAR T therapies *(modified from Miliotou and Papadopoulou, 2018)* (Miliotou and Papadopoulou, 2018).

Type of Toxicity	Cause
"On-target on-tumor"	Rapid oncolysis of large tumor Significant release of tumor cell components into the systemic circulation
"On-target off-tumor"	Engagement of a related antigen on healthy tissues
"Off-target off-tumor"	Inflammatory response outside of the targeted tumor tissue
Cytokine Release Syndrome (CRS)	Release of pro-inflammatory cytokines (IFN-γ, IL-6, TNF-α) by CAR T-cells, resulting in supra-physiological serum levels
Neurotoxicity	Systemic cytokines trafficking to the cerebrospinal fluid, thereby causing diffuse encephalopathy

Neurotoxicity is often observed concurrently with CRS, and is the result of increased circulating levels of cytokines crossing the blood brain barrier into to the cerebrospinal fluid (Prudent and Breitbart, 2017). This neurotoxicity presents as seizures, delirium, aphasia, and hallucinations, and is largely reversible (June et al., 2018). In rare instances, CRS can evolve into CAR T-cell related encephalopathy syndrome (CRES) or fulminant hemophagocytic lymphohistiocytosis (HLH; also known as macrophage activation syndrome) (Miliotou and Papadopoulou, 2018). Patients receiving tisangenlecleucel and axicabtagene ciloleucel during clinical trials reported neurotoxicity in percentages of 15% and 28%, respectively (Buechner et al., 2017; Neelapu et al., 2017).

Less common hazard considerations include "on-target off-tumor" toxicity resulting from target engagement of target antigen on non-pathogenic tissues (Morgan et al., 2010), anaphylaxis resulting from host recognition of infused foreign components (Maus et al., 2013), and the risk of insertional oncogenesis as observed in gene therapy of hematopoietic stem cells for X-linked severe combined immunodeficiency and chronic granulomatous disease (Hacein-Bey-Abina et al., 2008).

From an occupational perspective, common hazards include accidental punctures with needles or contaminated sharps, spills and splashes on the skin and mucus membranes, and inhalation exposure to infectious aerosols. Since workers tasked with manufacturing CAR T cells will be handling cells isolated from individual patients, the nature of the hazard will be dependent on the patients themselves (e.g., potentially infected with viruses pathogenic for humans such as HIV, adenovirus, etc.).

3.7.6. Occupational hazard and exposure considerations

Occupational hazards associated with manufacturing of CAR T cells are going to be similar to those encountered in any cell culture laboratory or medical laboratory where the handling of blood and body fluids occurs (Vormittag et al., 2018). Strict adherence to sterile technique and standard microbiological practices will ensure that occupational exposures are limited.

3.7.7. Occupational exposure banding guidance recommendation

A BSL is a biocontainment designation system with requirements intended to protect personnel from potentially harmful pathogenic exposure in a research or manufacturing environment (Table 4) (Control CfD and Prevention., 2009). Assigning an exposure control band is not appropriate for this modality. Rather, CAR T cell should only be handled by individuals trained in proper BSL procedures as recommended by the CDC for any human or other animal sourced material.

Table 4
Biosafety levels and examples.

Biosafety Level[a]	Applicable to Occupational Exposure Scenarios	Example: Microbes	Example: Cells
1	Low-risk microbes that pose little to no threat of infection in healthy adults	Nonpathogenic *Escherichia coli*	
2	Moderate-risk microbes that pose moderate hazards to laboratory personnel and the environment	*Staphylococcus aureus*; Shiga toxin producing *E. Coli*; Adenoviruses	Human and primate cells (CAR T cells)
3	Microbes (indigenous or exotic) that can cause serious or potentially lethal disease(s) through respiratory transmission	*Mycobacterium tuberculosis*	
4	High-risk microbes which pose a high risk of aerosol-transmitted infections and infections caused by these microbes are frequently fatal and without treatment or vaccines	Ebola virus	

[a] Note that enhanced control measures may be required depending on the strain and pathogenicity of the micro-organism being handled.

3.8. Oncolytic adenoviruses

3.8.1. Background

Oncolytic virotherapy is an emerging approach in the treatment of human cancer. Recently, the oncolytic virus Talimogene laherparepvec (T-VEC; Imlygic™) was approved for the treatment of advanced melanoma. T-VEC, an attenuated herpes simplex type 1 (HSV-1) encoding Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), provided evidence of the potential of locally delivered genetically modified replicating viruses as oncology agents, and opened the door for the development of viruses capable of tumor oncolysis via systemic administration (Rehman et al., 2016). Within this arena, development has focused primarily on the oncolytic adenoviruses given the fact that these non-enveloped, double-stranded DNA viruses possess genomes that are easily engineered, and because they exhibit low levels of pathogenicity following administration (Baker et al., 2018). While dozens of different adenoviruses have been described, they all share a common architecture consisting of an icosahedral capsid composed of up to seven different structural proteins. One of these, the fiber, is a trimeric protein located on each of the twelve vertices of the virion, which protrudes from the capsid like an antennae and directly influences adenovirus tropism (Russell, 2009).

3.8.2. How they work

Oncolytic adenoviruses function by selectively infecting and replicating in cancer cells while sparing non-cancerous cells. This selectively is accomplished via a number of subtle modifications in early adenoviral genes, and is summarized in the review by Baker et al., 2018 (Baker et al., 2018). The general viral cycle involves adenoviral recognition of its specific receptor on the cell surface thus triggering its internalization. Following this internalization, the adenovirus migrates through the microtubules and subsequently introduces the viral genome inside the nucleus. The adenovirus genome is composed of linear, double-stranded DNA of approximately 36 kilobases, which can be divided into early (E) and late (L) genes based upon their expression across the infection cycle (Seth and Higginbotham, 2000). While the L genes encode structural proteins, which package the viral DNA into the adenovirus virion during the final stages of replication, the E genes regulate viral replication itself, including entry of the virus into the host cell and entry of the virus genome into the nucleus. The proteins encoded by E1A specifically, are produced immediately after infection to modulate the cell cycle, recruit cellular proteins, and regulate the expression of cellular and viral genes (Wechman et al., 2016). The E1A protein binds the retinoblastoma protein (pRb) resulting in the release of E2F (E2 factor) and cell cycle arrest. The release of E2F subsequently triggers activation of viral genes that eventually lead to the generation of new virions, lysis of the infected cell, and spread of the viral progeny to adjacent cells (Garcia-Moure et al., 2017). Cancer cell lysis also releases tumor antigens, and pathogen- and damage-associated molecular pattern molecules (DAMPs) capable of stimulating tumor-infiltrating antigen presenting cells that activate innate and adaptive immune responses (Keller and Bell, 2016).

3.8.3. Marketed drugs

There exists and extensive number of completed or ongoing clinical trials utilizing adenoviruses. A 2018 search of clinicaltrials.gov found more than 180 clinical trials utilizing some form of adenovirus as cancer therapeutics (Baker et al., 2018). These trials have focused on a plethora of tumor types ranging from prostate carcinoma to glioblastoma multiforme, and have been examined as monotherapies or in combination with previously approved chemotherapeutics (Rosewell Shaw and Suzuki, 2016). While none have been approved to date by any Western country health authority, there is one oncolytic adenovirus that was approved in 2005 by the Chinese State Food and Drug Administration for the treatment of squamous cell cancer of the head and neck (HNC), and is marketed under the brand name Oncorine (Garcia-Moure et al., 2017; Garber, 2006). Oncorine (H101) is an E1B-55K/E3B-deleted oncolytic adenovirus that demonstrated efficacy and safety in HNC in a phase III trial, obtaining an overall response rate of nearly 80% in combination with cisplatin, with only mild flu-like symptoms as side effects (Xia et al., 2004).

3.8.4. ADME

Clinical studies on oncolytic adenoviruses have demonstrated varied PK depending on the route of administration, adenovirus serotype and associated genetic modifications, such that generalizations regarding pharmacokinetic (PK) parameters cannot be made. For example, in a Phase 1 study of enadenotucirev (a group B Ad11p/Ad3 chimeric oncolytic adenovirus) administered intravenously to patients with epithelial solid tumors, the half-life was short (16.7 min) and independent of dose and administration frequency (Machiels et al., 2019). Post-infusion viral shedding (i.e., release of adenovirus from injection sites and patient secretions) manifested as buccal shedding and rectal shedding (both of which were related to dose level), and to a lesser extent, urine shedding. In a second example, a Phase 1 dose escalation study examined the safety and host immune response of telomelysin (OBP-301) following a single intratumoral injection in patients with advanced solid tumors (Phadke, 2008). Telomelysin is a telomerase-specific replication-selective adenovirus in which the human telomerase reverse transcriptase promotor element drives expression of E1A/E1B genes linked with an internal ribosome entry site. This study indicated that despite intratumoral dosing, viral DNA was detected in 5 of 9 patient plasma samples, as early as 30 min and as late as 14 days post-treatment. Viral DNA was also detected in the sputum of one patient, indicating systemic dissemination following intratumoral injection (Phadke, 2008). Systemic dissemination of oncolytic adenoviral DNA via vascular transduction has also been demonstrated in a study examining post-mortem tissues of cancer patients treated with this modality either intratumorally or intravenously, and whose deaths were caused by disease progression rather than the treatment vector (Koski et al., 2015). Oncolytic adenoviral DNA was recovered in a wide array of tissues, including both injected and non-injected tumors and various normal tissues, including the brain.

3.8.5. Health hazards as a class/modality associated with therapeutic use

Generally, the use of oncolytic adenoviruses appears to be reasonably safe following local administration (i.e., intratumoral) and lower systemic doses, although the development of newer generations of adenoviruses expressing transgenes and possessing altered capsids or different promoters could alter the safety profile (Buijs et al., 2015). Viral shedding of engineered adenovirus vectors could theoretically result in homologous recombination between wildtype adenoviruses of the same subgroup, leading to new wildtype adenoviruses that possess transgenes or have expanded tissue tropism due to retargeting strategies (Buijs et al., 2015; Singh et al., 2013). To date, no such recombination events have been observed in clinical trials.

Given the mechanism of action of oncolytic adenoviruses, one might consider CRS an outcome of concern. However, in the thousands of patients that have received adenoviruses therapeutically, only one patient (who consequently, had an underlying metabolic disorder) has died as a result of CRS (Sibbald, 2001). Based on this prior extensive clinical experience, the risk of severe CRS and toxicity is generally deemed to be minimal, especially considering the neoantigens expressed by the virus are not typically present in normal tissue and therefore, cross-reactive T-cell responses are unlikely to occur (Larson et al., 2018).

3.8.6. Occupational hazard and exposure considerations

Occupational exposure to an adenovirus is generally through the upper respiratory tract via aerosol exposure, although other potential routes of exposure include via mucus membranes (splash of virus to eye, nose, mouth), parenteral (needle stick or sharp object injury) and contact with non-intact skin (Larson et al., 2018). In general, adenovirus infection most commonly causes respiratory illness, although, depending on the infecting serotype, they may cause other illnesses such as gastroenteritis, conjunctivitis, cystitis, and rash (Stanford. Stanford Enviro, 2020). Adenovirus infection of the respiratory systems typically can present as a spectrum of ailments ranging from the common cold syndrome to pneumonia, croup, and bronchitis. In terms of exposure scenarios specifically, special consideration must be given to the potential for viral shedding and human-to-human transmission. In the clinical setting, viral shedding can occur from injection sites and patient excretions, and prevalence has been demonstrated to increase with higher doses and systemic administration (Kimball et al., 2010; Keedy et al., 2008; Tian et al., 2009). Preclinically, viral shedding could result in exposure via contact with animal secreta, excreta and bedding.

Pregnant individuals and those who are severely immunocompromised are particularly susceptible to adenovirus exposure and should exercise extreme caution when handling adenoviruses, as infection could lead to systemic disease (e.g. hepatitis). There is a paucity of data in terms of occupational exposures to oncolytic adenoviruses. However, a study in which health-care workers involved in the aerosolized administration of adeno-associated virus (AAV) during a Phase II cystic fibrosis study determined that individuals were exposed to an estimated 0.0006% of the administered doses based on airborne vector particle concentration. At this level of exposure, the prevalence of symptoms (typically associated with adenovirus exposure) was very low, the spectrum of symptoms was similar in both active and control health care workers, and there were no reported negative health effects (Croteau et al., 2004). It is assumed that oncolytic adenoviruses and AAVs would behave similarly in this exposure scenario. Therefore, if proper handling precautions and engineering controls are implemented as described in the proceeding section, occupational exposure is expected to be limited.

While the focus here has been placed on adenoviruses specifically, there are a number of other oncolytic virus platforms in development for the treatment of cancer including herpes simplex virus 1, measles virus, coxsackievirus, and poliovirus, among others (Buijs et al., 2015). Occupational exposure considerations as outlined for adenoviruses previously would be applicable to these other virus types as well.

3.8.7. Occupational exposure banding guidance recommendation

Adenoviruses should be handled as dictated by the applicable Biological Safety Level (BSL) (See Table 4) (Control CfD and Prevention., 2009). For other virus types, the appropriate BSL as outlined in the Biosafety in Microbiological and Biomedical Laboratories guidance prepared by the Centers for Disease Control and the National Institutes of Health should be followed (Control CfD and Prevention., 2009).

3.9. Engineered bacteria

3.9.1. Background

Bacteria can be genetically modified (GM) to produce a continuous and inexpensive supply of proteins/molecules such as human hormones, interleukins and antibodies within specific organs or tissues (Pinero-Lambea et al., 2015). An enhanced understanding of the role of the human gut microbiome in health and diseases has increased interest in the use of live bio-therapeutic products (LBPs), such as GM bacteria, for the treatment or prevention of disease. Also important, especially in the context of developing countries, is that GM bacteria can be administered orally, which makes the requirement for hygienic syringes and needles unnecessary. The use of this technology for vaccines is in the spotlight since, in addition to the ease of oral administration, GM bacteria are relatively inexpensive to propagate/manufacture and transport (resistant to poor refrigeration), and thus the ongoing revolution in GM bacteria for vaccination fits well with the World Health Organization (WHO) agenda and recommendations.

3.9.2. How they work

GM bacteria serve as drug delivery systems, which, upon oral administration, can carry the drug and deliver it to a local environment such as the gut or mucosa, without the need for systemic exposure. GM bacteria are being regarded as a technologically viable, economically-feasible, safe delivery modality for drugs/proteins to localized areas in the body (Ferreira et al., 2017). The insertion of plasmid vectors, which encode proteins such as enzymes, antibodies, antigens and cytokines into living bacteria, enables these GM bacteria to produce or deliver the therapeutic proteins/molecules to the target site. GM bacteria have also been designed to convert pro-drugs to their active form at the localized disease site (Pinero-Lambea et al., 2015). GM bacteria can bypass problems associated with conventional cancer chemotherapies, such as poor selectivity and limited tumor penetrability, and can be finely engineered to sense and respond to the tumor microenvironment (Forbes, 2010). Local delivery of recombinant proteins via GM bacteria in affected organs also has many advantages as systemic side effects are generally avoided.

3.9.3. Marketed drugs

Currently, there are no approved GM bacterial therapeutics. Many have been studied in clinical trials and been shown to be promising components of therapies for numerous cancer types and immune-related diseases, while exhibiting a low incidence of adverse events (Pinero-Lambea et al., 2015; Ferreira et al., 2017). Many of the GM bacteria utilized in clinical trials are similar to those sold over the counter as probiotics (Dreher-Lesnick et al., 2017) and natural isolates obtained from the microbiota of healthy individuals. They are most often lactic acid bacteria (LAB) and to a lesser extent *Escherichia coli* strains (Pinero-Lambea et al., 2015).

3.9.4. ADME

Microbes are commonly ingested via a variety of fermented foods and drinks. They then go on to live in the intestinal milieu. Once a new host has ingested the bacteria, the bacteria must colonize otherwise they will rapidly transit through the gastrointestinal system and be eliminated in fecal matter. Additionally, bacteria which have successfully colonized the intestinal environment by establishing a niche and reaching replication levels that ensure stability and survival can shed

from the host into fecal matter (Browne et al., 2017). Once it has entered the external environment, there is a potential that the GM bacteria can enter a new susceptible host.

3.9.5. Health hazards as a class/modality associated with therapeutic use

The main health hazards associated with GM bacteria are the risk of infection and the risk of transient or stable transfer of identified genes of concern (e.g. antibiotic resistance genes) in the LBP to another species present in host sites exposed to product colonization.

3.9.6. Occupational hazard and exposure considerations

Bacteria are key elements for human health as evinced by the gut microbiota and the numerous health disorders in axenic animals (Pinero-Lambea et al., 2015). The occupational safety assessment of a novel bacterial species should take into account information on the bacterial strain(s) and source(s) of the strain (e.g. original donor), the proposed subject population, mechanism of action, the intended route of administration and the delivery method. If there are genetic modifications to the strain, the stability of those genetic modifications should be taken into account and assessed. As it is important to ensure product-related infections can be treated should they arise, strain characterization information including details about the presence of virulence factors or toxins and the strain's antibiotic resistance profile (inclusive of knowledge of any antibiotic resistance genes present in the GM bacteria) should be assessed/considered.

3.9.7. Occupational exposure banding guidance recommendation

Given that GM bacteria are microbes, they should be handled as dictated by the applicable BSL (Control CfD and Prevention., 2009).

3.10. Vaccines

3.10.1. Background

Vaccines provide the main method of prophylaxis against pandemic viruses and other infectious diseases. The introduction of human vaccines has had a tremendous impact on global health by dramatically reducing the mortality and morbidity caused by infectious diseases. Vaccination is considered one of the most cost effective and successful medical interventions ever introduced. Vaccines have inevitably prevented diseases, complications, and the death of millions of people by protecting against many deadly and debilitating infectious diseases including smallpox and polio (Kallerup and Foged, 2015). The World Health Organization (WHO) currently recommends routine immunization against 22 different diseases (WHO, 2019).

3.10.2. How they work

The ideal vaccine elicits the exact immune response that occurs during natural infection, safely inducing a strong humoral and cellular immune response. Vaccines work by mimicking disease agents and stimulating the immune system to build up defenses against them. Vaccines are generally created to express one or more antigens present on a pathogen to prime an individual's immune system, so that if the individual is exposed to the pathogen in the future, the immune system will respond swiftly with a specific defense. Briefly, antigen-presenting cells (APCs; e.g., dendritic cells, macrophages) take up and process the pathogen-specific antigen(s) and present them to $CD4^+$ T cells via the MHC class II pathway and then to B cells, ultimately resulting in the production of antibodies. For most infectious diseases, primary protection is mediated by existing antibodies, whereas for intracellular pathogens (e.g. mycobacterium tuberculosis), protection is mediated by MHC class I-restricted CD8 T cell responses. The goal of vaccination is to produce a memory of the vaccine antigen, so that if an individual is exposed to the pathogen in the future, the memory cells will recognize it and the immune system will be able to respond more effectively than if it had never encountered the pathogen.

3.10.3. Marketed drugs

A few examples of marketed vaccines include Flumist® Quadrivalent, Gardasil® and BioThrax®. Flumist® Quadrivalent, a vaccine against influenza, contains a live attenuated influenza virus that contains four vaccine virus strains for administration via an intranasal spray (MedImmune. FluMist Quadri, 2013). Gardasil®, a vaccine targeted against human papillomavirus (HPV), is a recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18 and is administered with Alum adjuvant (Siddiqui and Perry, 2006). BioThrax®, a subunit vaccine for Anthrax (Bacillus anthraxis), consists of an avirulent, nonencapsulated strain of Bacillus anthracis and proteins and is administered with Alum adjuvant (BioSolutions, 2013).

Several vaccine platforms along with the relevant occupational hazards and control guidance as well as examples of currently marketed vaccines are presented in Table 5. Coronavirus disease or COVID-19 vaccine candidates exist for each of the vaccine platforms and several of these are noted (Le et al., 2020). The WHO's authoritative and continually updated list of COVID-19 vaccine candidates is located at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

3.10.4. ADME

PK studies are generally not required or conducted for vaccines because the kinetic properties of antigens do not provide useful information for determining dose recommendations. Differences in distribution, persistence and elimination of the components of a vaccine can be attributed to several factors such as the route of administration, the number of injections, the quantity of antigen and the species under study (Faurez et al., 2010). Whatever the route of administration, the site of injection is the area where the vaccine components tend to remain the most concentrated and persist the longest, however vaccine components have been observed in organs throughout the body including immune cells and the blood (Faurez et al., 2010). Vaccinated persons have been shown to shed vaccine viruses, however the shed live attenuated viruses are generally stable and do not revert to virulent strains (Fiore et al., 2009).

3.10.5. Health hazards as a class/modality associated with therapeutic use

There are safety concerns associated with various vaccine platforms. Although attenuated vaccines elicit long-lasting immunity, safety issues including the administration of live viral or bacterial components and their capacity to replicate, infect immunocompromised individuals, and revert to pathogenic forms are of concern. For example, whole virus vaccines are considered too reactive, particularly in young children (Wood and Robertson, 2004). In the case of plasmid DNA, there is a concern that the DNA vaccine could possibly integrate into host genomes, increasing the risk of malignancy (via insertional mutagenesis) (Kim and Jacob, 2009). Adjuvanated vaccines have only recently been licensed so there remains some uncertainty regarding the safety of some adjuvants in humans (Keitel and Atmar, 2009). Additionally, adjuvanted formulations typically elicit a higher frequency of injection site, and occasionally systemic, reactions when compared with non-adjuvanted formulations (Keitel and Atmar, 2009). The possibility of adverse reactions increase when multiple doses are required to provide immunity.

Both aerosol-administered and intradermally administered vaccines have been well tolerated and immunogenic. Respiratory adverse events are rare and mild. Intradermal vaccines have been associated with expected mild local injection-site reactions (Satti et al., 2014). Common adverse effects in vaccine recipients include fatigue and headache. In studies with FluMist®, adverse effects included runny nose or nasal congestion, headache, sore throat, tiredness/weakness, muscle aches, cough or chills and rarely wheezing that required bronchodilator therapy or that was associated with significant respiratory symptoms (Fiore et al., 2009).

Table 5
Vaccine platforms, associated occupational hazard and exposure control guidance, and banding paradigms[a].

Vaccine Platform	Potential Vaccine Components	Example(s)[b]	Occupational Hazards and Exposure Control Guidance	Banding Paradigm[c]
Live Attenuated Virus or Bacteria	Deoptimized live attenuated virus or bacteria	Marketed: Flumist® Quadrivalent (Influenza) COVID-19 Candidates in Development: Attenuated Influenza expressing an antigenic portion of the Spike protein	See Section 3.8 (Oncolytic adenoviruses), 3.9 (Engineered Bacteria) and Section 3.10 (Vaccines)	BSLs (Table 4)
Inactivated Virus	Adenovirus, measles, influenza or other viral vector	Marketed: IPOL® (Polio) COVID-19 Candidates in Development: Whole-Virion Inactivated	See Section 3.8 (Oncolytic adenoviruses) and Section 3.10 (Vaccines)	BSLs (Table 4)
Protein Subunit	Peptide, S protein, peptide antigens	Marketed: BioThrax® (Anthrax) COVID-19 Candidates in Development: Recombinant protein (RBD-Dimer) + Adjuvant	See Sections 3.1 (Small molecules), 3.3 (Peptides), 3.4 (Biologics), 3.9 (Engineered Bacteria) and Section 3.10 (Vaccines)	Small molecule banding paradigm (Table 1) or BCCs (Table 2)
DNA	DNA, Plasmid DNA	Marketed: None currently approved for use in humans; West Nile-Innovator DNA vaccine for equines (West Nile Virus) COVID-19 Candidates in Development Include: Spike DNA vaccine + Adjuvant	See Section 3.2 (Oligonucleotides) and Section 3.10 (Vaccines)	Small molecule banding paradigm (Table 1)
RNA	mRNA, small activating RNA, encapsulated mRNA	Marketed: None currently approved COVID-19 Candidates in Development: LNP-encapsulated mRNA	See Section 3.2 (Oligonucleotides) and Section 3.10 (Vaccines)	Small molecule banding paradigm (Table 1)
Virus-like particle (VLP)	Proteins	Marketed: Gardasil® (human papillomavirus) COVID-19 Candidates in Development: Plant-derived VLP + Adjuvant	See Section 3.1 (Small Molecules) and Section 3.10 (Vaccines)	Small molecule banding paradigm (Table 1) or BCCs (Table 2)

[a] Not an exhaustive list.
[b] COVID-19 Candidate information obtained from the WHO's authoritative and continually updated list of COVID-19 vaccine candidates located at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 07August 2020).
[c] Note that BCCs are utilized at BMS, however alternative banding paradigms for biologics are also used in the pharmaceutical industry which are equally effective in controlling exposures.

3.10.6. Occupational hazard and exposure considerations

Many vaccines are expected to be avirulent in humans. Inactivated pandemic influenza vaccines present no biosafety risks provided that the results of the inactivation steps show complete virus inactivation, as the viral vaccine is rendered incapable of replication (Organization WH, 2005). Concerns arise where workers are immunologically naive to a virus and potentially susceptible to infection. In the instances where viruses are utilized, there are concerns around human infection with the vaccine virus during manufacturing and of a subsequent outbreak originating from the manufacturing plant (Organization WH, 2005).

Inhalation exposure to live viruses or bacteria are of concern. Upon inhalation, live attenuated viruses have the potential to replicate in the mucosa of the respiratory tract (Chen and Subbarao, 2009). Human-to-human transmission is expected to be unlikely since replication is attenuated and the virus titers would be below those considered necessary for human infection (Organization WH, 2005). Potential adverse effects may be at worst, similar to those observed upon intranasal administration of live attenuated influenza, which consist of some effects of local viral replication (e.g., nasal congestion). With the exception of surrogate viruses, the use of wild type pandemic-like viruses to develop pandemic vaccine strains presents considerable biosafety risks to personnel in vaccine development and manufacturing facilities (Organization WH, 2005). Additionally, viruses may be expected to survive for at least a short time (hours) on surfaces and thus provide a potential means of infection for workers (Organization WH, 2005). Therefore, the wild-type pandemic-like viruses present the greatest occupational health concern.

3.10.7. Occupational exposure banding guidance recommendation

Vaccine production facilities are designed to maintain the sterility of the product. Therefore, although there is opportunity to be exposed to the virus and/or antigens, occupational exposures are expected to be limited. The WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines presents guidance to vaccine manufacturers on the safe production of influenza vaccines (Organization WH, 2005). According to the WHO guideline, all laboratory procedures involving live highly pathogenic influenza viruses should take place at a high level of biological containment (e.g., BSL3 and above, as recommended by WHO and national regulatory bodies). Stringent vaccine biosafety control measures with specific enhancements, defined as BSL2 enhanced (BSL2-e; pandemic influenza vaccine) and BSL3 enhanced (BSL3-e; pandemic influenza vaccine) are designed to manage the risk from vaccine production and quality control using such viruses during the pre-pandemic or inter-pandemic period (Organization WH, 2005). In the United Kingdom, it is necessary to use BSL4 facilities, but in other parts of the world (e.g. United States) working with highly pathogenic avian influenza (HPAI) viruses is acceptable under BSL3-e (Wood and Robertson, 2004). Note that while this guidance exists, a risk assessment should be performed that will depend on the nature of the strain and the pandemic period declared by WHO (Organization WH, 2005).

4. Conclusion

Novel therapeutic drugs and technologies of increasing complexity and potency are being developed and handled throughout pharmaceutical research, development and manufacturing organizations and clinics. As biological processes become elucidated and novel drug platforms continue to be discovered, classical small-molecule approaches are not always appropriate or adequate and so other types of modalities are required to address these targets (e.g. protein–protein and protein–nucleic acid interactions). From an occupational safety perspective, this means staying current with the emerging literature on the hazards observed and expected with therapeutics spanning multiple modalities. Occupational safety professionals must be proactive and aware of the pharmacological, toxicological and physicochemical characteristics of the new modalities residing within their respective drug development pipelines to ensure occupational exposures are appropriately controlled and the risk of adverse effects, both pharmacological and toxicological, in the workplace is minimized. Occupational exposure control banding systems represent an acceptable approach to ensuring the safe handling of many new modalities, however it is important to be aware that certain modalities do not fit historical banding paradigms and require other means of classification, such as BSLs or BCCs.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

Ader, A.W., Farris, J.P., Ku, R.H., 2005. Occupational health categorization and compound handling practice systems—roots, application and future. J. Chem. Health Saf. 12 (4), 20–26. https://doi.org/10.1021/acs.chas.8b12407.

Agency, E.M., 2014. Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities.

Alton, E.W., Boushey, H.A., Garn, H., Green, F.H., Hodges, M., Martin, R.J., et al., 2012. Clinical expert panel on monitoring potential lung toxicity of inhaled oligonucleotides: consensus points and recommendations. Nucleic Acid Therapeut. 22 (4), 246–254. https://doi.org/10.1089/nat.2012.0345. Epub 2012/07/20, PubMed PMID: 22809313; PubMed Central PMCID: PMCPMC3426204.

Autio, K.A., Boni, V., Humphrey, R.W., Naing, A., 2020. Probody therapeutics: an emerging class of therapies designed to enhance on-target effects with reduced off-tumor toxicity for use in immuno-oncology. Clin. Canc. Res. 26 (5), 984–989.

Baker, A.T., Aguirre-Hernandez, C., Hallden, G., Parker, A.L., 2018. Designer oncolytic adenovirus: coming of age. Cancers 10 (6). https://doi.org/10.3390/cancers10060201. Epub 2018/06/16, PubMed PMID: 29904022; PubMed Central PMCID: PMCPMC6025169.

Baldo, B.A., 2015. Chimeric fusion proteins used for therapy: indications, mechanisms, and safety. Drug Saf. 38 (5), 455–479. https://doi.org/10.1007/s40264-015-0285-9. Epub 2015/04/03, PubMed PMID: 25832756.

Basketter, D.A., Kruszewski, F.H., Mathieu, S., Kirchner, D.B., Panepinto, A., Fieldsend, M., et al., 2015. Managing the risk of occupational allergy in the enzyme detergent industry. J. Occup. Environ. Hyg. 12 (7), 431–437.

Beck, A., Goetsch, L., Dumontet, C., Corvaia, N., 2017. Strategies and challenges for the next generation of antibody-drug conjugates. Nat. Rev. Drug Discov. 16 (5), 315–337. https://doi.org/10.1038/nrd.2016.268. Epub 2017/03/18, PubMed PMID: 28303026.

Bercu, J.P., Dolan, D.G., 2013. Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul. Toxicol. Pharmacol. 65 (1), 162–167. https://doi.org/10.1016/j.yrtph.2012.06.012. Epub 2012/06/27, PubMed PMID: 22732128.

Berman, C.L., Barros, S.A., Galloway, S.M., Kasper, P., Oleson, F.B., Priestley, C.C., et al., 2016. OSWG recommendations for genotoxicity testing of novel oligonucleotide-based therapeutics. Nucleic Acid Therapeut. 26 (2), 73–85. https://doi.org/10.1089/nat.2015.0534. Epub 2016/03/16, PubMed PMID: 26978711.

BioSolutions, E., 2013. Biothrax Package Insert. Emergent BioSolutions Rockville, MD.

Bonifant, C.L., Jackson, H.J., Brentjens, R.J., Curran, K.J., 2016. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics 3, 16011. https://doi.org/10.1038/mto.2016.11. Epub 2016/09/15, PubMed PMID: 27626062; PubMed Central PMCID: PMCPMC5008265.

Bos, J.D., Meinardi, M.M., 2000. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp. Dermatol.: Viewpoint 9 (3), 165–169.

Brennan, F.R., Morton, L.D., Spindeldreher, S., Kiessling, A., Allenspach, R., Hey, A., et al., 2010. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. mAbs 2 (3), 233–255. https://doi.org/10.4161/mabs.2.3.11782. Epub 2010/04/28, PubMed PMID: 20421713; PubMed Central PMCID: PMCPMC2881251.

Brinkmann, U., Kontermann, R.E., 2017. The making of bispecific antibodies. mAbs 9 (2), 182–212. https://doi.org/10.1080/19420862.2016.1268307. Epub 2017/01/11, PubMed PMID: 28071970; PubMed Central PMCID: PMCPMC5297537.

Brown, C.E., Badie, B., Barish, M.E., Weng, L., Ostberg, J.R., Chang, W.C., et al., 2015. Bioactivity and safety of IL13Ralpha2-redirected chimeric antigen receptor CD8+ T cells in patients with recurrent glioblastoma. Clin. Canc. Res. : Off. J. Am. Assoc. Canc. Res 21 (18), 4062–4072. https://doi.org/10.1158/1078-0432.CCR-15-0428. Epub 2015/06/11, PubMed PMID: 26059190; PubMed Central PMCID: PMCPMC4632968.

Browne, H.P., Neville, B.A., Forster, S.C., Lawley, T.D., 2017. Transmission of the gut microbiota: spreading of health. Nat. Rev. Microbiol. 15 (9), 531–543. https://doi.org/10.1038/nrmicro.2017.50. Epub 2017/06/12, PubMed PMID: 28603278.

Buechner, J., Grupp, S., Maude, S., Boyer, M., Bittencourt, H., Laetsch, T., et al., 2017. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): update to the interim analysis. Clin. Lymphoma, Myeloma & Leukemia 17, S263–S264. https://doi.org/10.1016/j.clml.2017.07.030.

Buijs, P.R., Verhagen, J.H., van Eijck, C.H., van den Hoogen, B.G., 2015. Oncolytic viruses: from bench to bedside with a focus on safety. Hum. Vaccines Immunother. 11 (7), 1573–1584. https://doi.org/10.1080/21645515.2015.1037058. Epub 2015/05/23, PubMed PMID: 25996182; PubMed Central PMCID: PMCPMC4514197.

Cai, H., 2018. Therapeutic monoclonal antibodies approved by FDA in 2017. MOJ Immunology 6. https://doi.org/10.15406/moji.2018.06.00198.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Chebekoue, S.F., Krishnan, K., 2017. Derivation of occupational thresholds of toxicological concern for systemically acting noncarcinogenic organic chemicals. Toxicol. Sci. 160 (1), 47–56.

Chebekoue, S.F., Krishnan, K., 2019. Derivation of internal dose-based thresholds of toxicological concern for occupational inhalation exposure to systemically acting organic chemicals. J. Occup. Environ. Hyg. 16 (4), 308–319.

Chen, G.L., Subbarao, K., 2009. Live Attenuated Vaccines for Pandemic Influenza. Vaccines for Pandemic Influenza. Springer, pp. 109–132.

Chen, C., Wang, Z., Zhang, Z., Liu, X., Kang, S.S., Zhang, Y., et al., 2018. The prodrug of 7,8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease, 3. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 115, pp. 578–583. https://doi.org/10.1073/pnas.1718683115. Epub 2018/01/04, PubMed PMID: 29295929; PubMed Central PMCID: PMCPMC5777001.

Chmielewski, M., Hombach, A.A., Abken, H., 2013. Antigen-specific T-cell activation independently of the MHC: chimeric antigen receptor-redirected T cells. Front. Immunol. 4, 371. https://doi.org/10.3389/fimmu.2013.00371. Epub 2013/11/26, PubMed PMID: 24273543; PubMed Central PMCID: PMCPMC3822734.

Clarke, B.N., 2018. PET Radiopharmaceuticals: what's new, what's reimbursed, and what's next? J. Nucl. Med. Technol. https://doi.org/10.2967/jnmt.117.205021. Epub 2018/02/14, PubMed PMID: 29438008.

Control CfD, Prevention. Biosafety in Microbiological and Biomedical Laboratories (BMBL), 2009. US Government Printing Office, St Louis, MO.

Control CfD, 2015. CDC Radiation Safety.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard–a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276. https://doi.org/10.1016/s0015-6264(76)80522-6. Epub 1978/06/01, PubMed PMID: 357272.

Croteau, G.A., Martin, D.B., Camp, J., Yost, M., Conrad, C., Zeitlin, P.L., et al., 2004. Evaluation of exposure and health care worker response to nebulized administration of tgAAVCF to patients with cystic fibrosis. Ann. Occup. Hyg. 48 (8), 673–681. https://doi.org/10.1093/annhyg/meh066. Epub 2004/10/28, PubMed PMID: 15507460.

Dahlen, E., Veitonmaki, N., Norlen, P., 2018. Bispecific antibodies in cancer immunotherapy. Ther Adv Vaccines Immunother 6 (1), 3–17. https://doi.org/10.1177/2515135518763280. Epub 2018/07/13, PubMed PMID: 29998217; PubMed Central PMCID: PMCPMC5933537.

de Lemos, M.L., Badry, N., Kletas, V., Fabbro, J., Tew, A., 2018. Safe handling of monoclonal antibodies: too large to be hazardous? J. Oncol. Pharm. Pract. 24 (3), 218–220. https://doi.org/10.1177/1078155217698846. Epub 2017/12/30, PubMed PMID: 29284346.

Derelanko, M.J., 2017. The Toxicologist's Pocket Handbook. CRC Press.

Desnoyers, L.R., Vasiljeva, O., Richardson, J.H., Yang, A., Menendez, E.E., Liang, T.W., et al., 2013. Tumor-specific activation of an EGFR-targeting probody enhances therapeutic index. Sci. Transl. Med. 5 (207) https://doi.org/10.1126/scitranslmed.3006682, 207ra144. Epub 2013/10/18, PubMed PMID: 24132639.

Directive C, 2013. 59/Euratom of 5 December 2013 Laying Down Basic Safety Standards for Protection against the Dangers Arising from Exposure to Ionising Radiation, and Repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. Euratom.

Dolan, D.G., Naumann, B.D., Sargent, E.V., Maier, A., Dourson, M., 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul. Toxicol. Pharmacol. 43 (1), 1–9. https://doi.org/10.1016/j.yrtph.2005.06.010. Epub 2005/08/16, PubMed PMID: 16099564.

Dougherty, T.J., Pucci, M.J., 2011. Antibiotic Discovery and Development. Springer US.

Drake, P.M., Rabuka, D., 2017. Recent developments in ADC technology: preclinical studies signal future clinical trends. BioDrugs 31 (6), 521–531. https://doi.org/10.1007/s40259-017-0254-1. Epub 2017/11/10, PubMed PMID: 29119409; PubMed Central PMCID: PMCPMC5696438.

Dreher-Lesnick, S.M., Stibitz, S., Carlson Jr., P.E., 2017. Regulatory considerations for development of live biotherapeutic products as drugs. Microbiol. Spectr. 5 (5) https://doi.org/10.1128/microbiolspec. Epub 2017/10/05, BAD-0017-2017. PubMed PMID: 28975881.

Ducry, L., Stump, B., 2010. Antibody-drug conjugates: linking cytotoxic payloads to monoclonal antibodies. Bioconjugate Chem. 21 (1), 5–13. https://doi.org/10.1021/bc9002019. Epub 2009/09/23, PubMed PMID: 19769391.

Dumont, J.A., Bitonti, A.J., Clark, D., Evans, S., Pickford, M., Newman, S.P., 2005. Delivery of an erythropoietin-Fc fusion protein by inhalation in humans through an immunoglobulin transport pathway. J. Aerosol Med. 18 (3), 294–303. https://doi.org/10.1089/jam.2005.18.294. Epub 2005/09/27, PubMed PMID: 16181004.

EPA, 2020. United States Environmental Protection Agency: Federal Guidance for Radiation Protection.
Faurez, F., Dory, D., Le Moigne, V., Gravier, R., Jestin, A., 2010. Biosafety of DNA vaccines: new generation of DNA vectors and current knowledge on the fate of plasmids after injection. Vaccine 28 (23), 3888–3895.
Fellner, R.C., Terryah, S.T., Tarran, R., 2016. Inhaled protein/peptide-based therapies for respiratory disease. Mol Cell Pediatr 3 (1), 16. https://doi.org/10.1186/s40348-016-0044-8. Epub 2016/04/22, PubMed PMID: 27098663; PubMed Central PMCID: PMCPMC4839019.
Ferreira, A.K., Mambelli, L.I., Pillai, S.Y., 2017. Intervening in disease through genetically-modified bacteria. Best Pract. Res. Clin. Gastroenterol. 31 (6), 693–697.
Ferri, N., Bellosta, S., Baldessin, L., Boccia, D., Racagni, G., Corsini, A., 2016. Pharmacokinetics interactions of monoclonal antibodies. Pharmacol. Res. 111, 592–599. https://doi.org/10.1016/j.phrs.2016.07.015. Epub 2016/07/21, PubMed PMID: 27438459.
Fiore, A.E., Bridges, C.B., Cox, N.J., 2009. Seasonal Influenza Vaccines. Vaccines for Pandemic Influenza. Springer, pp. 43–82.
Food, Administration D, 2018. Yescarta Package Insert.
Forbes, N.S., 2010. Engineering the perfect (bacterial) cancer therapy. Nat. Rev. Canc. 10 (11), 785–794.
Fosgerau, K., Hoffmann, T., 2015. Peptide therapeutics: current status and future directions. Drug Discov. Today 20 (1), 122–128. https://doi.org/10.1016/j.drudis.2014.10.003. Epub 2014/12/03, PubMed PMID: 25450771.
Garber, K., 2006. China approves world's first oncolytic virus therapy for cancer treatment. J. Natl. Cancer Inst. 98 (5), 298–300. https://doi.org/10.1093/jnci/djj111. Epub 2006/03/02, PubMed PMID: 16507823.
Garcia-Alonso, S., Ocana, A., Pandiella, A., 2018. Resistance to antibody-drug conjugates. Canc. Res. 78 (9), 2159–2165. https://doi.org/10.1158/0008-5472.CAN-17-3671. Epub 2018/04/15, PubMed PMID: 29653942.
Garcia-Moure, M., Martinez-Velez, N., Patino-Garcia, A., Alonso, M.M., 2017. Oncolytic adenoviruses as a therapeutic approach for osteosarcoma: a new hope. J Bone Oncol 9, 41–47. https://doi.org/10.1016/j.jbo.2016.12.001. Epub 2017/12/12, PubMed PMID: 29226089; PubMed Central PMCID: PMCPMC5715440.
Garg, A., Balthasar, J.P., 2007. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. J. Pharmacokinet. Pharmacodyn. 34 (5), 687–709. https://doi.org/10.1007/s10928-007-9065-1. Epub 2007/07/20, PubMed PMID: 17636457.
Garrido, F., Aptsiauri, N., Doorduijn, E.M., Garcia Lora, A.M., van Hall, T., 2016. The urgent need to recover MHC class I in cancers for effective immunotherapy. Curr. Opin. Immunol. 39, 44–51. https://doi.org/10.1016/j.coi.2015.12.007. Epub 2016/01/23, PubMed PMID: 26796069; PubMed Central PMCID: PMCPMC5138279.
Garrod, A.N., Rajan-Sithamparanadarajah, R., 2003. Developing COSHH Essentials: dermal exposure, personal protective equipment and first aid. Ann. Occup. Hyg. 47 (7), 577–588. https://doi.org/10.1093/annhyg/meg089. Epub 2003/10/08, PubMed PMID: 14530184.
Gould, J., Callis, C.M., Dolan, D.G., Stanard, B., Weideman, P.A., 2016. Special endpoint and product specific considerations in pharmaceutical acceptable daily exposure derivation. Regul. Toxicol. Pharmacol. 79 (Suppl. 1), S79–S93. https://doi.org/10.1016/j.yrtph.2016.05.022. Epub 2016/05/29, PubMed PMID: 27233924.
Gould, J.C., Carvajal, I., Davidson, T., Graham, J., Hillegass, J., Julien, S., et al., 2018. Bioavailability of protein therapeutics in rats following inhalation exposure: relevance to occupational exposure limit calculations. Regul. Toxicol. Pharmacol. 100, 35–44. https://doi.org/10.1016/j.yrtph.2018.10.003. Epub 2018/10/07, PubMed PMID: 30291877.
Guideline, I.H.T. (Ed.), 2018. Assessment and Control of Dna Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic RISK M7. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH), Geneva.
Guimond, A., Viau, E., Aube, P., Renzi, P.M., Paquet, L., Ferrari, N., 2008. Advantageous toxicity profile of inhaled antisense oligonucleotides following chronic dosing in non-human primates. Pulm. Pharmacol. Therapeut. 21 (6), 845–854. https://doi.org/10.1016/j.pupt.2008.08.001. Epub 2008/09/02, PubMed PMID: 18761414.
Hacein-Bey-Abina, S., Garrigue, A., Wang, G.P., Soulier, J., Lim, A., Morillon, E., et al., 2008. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J. Clin. Invest. 118 (9), 3132–3142. https://doi.org/10.1172/JCI35700. Epub 2008/08/09, PubMed PMID: 18688285; PubMed Central PMCID: PMCPMC2496963.
Halsen, G., Kramer, I., 2011. Assessing the risk to health care staff from long-term exposure to anticancer drugs–the case of monoclonal antibodies. J. Oncol. Pharm. Pract. 17 (1), 68–80. https://doi.org/10.1177/1078155210376847. Epub 2010/07/30, PubMed PMID: 20667850.
Han, T.H., Zhao, B., 2014. Absorption, distribution, metabolism, and excretion considerations for the development of antibody-drug conjugates. Drug Metab. Dispos. 42 (11), 1914–1920. https://doi.org/10.1124/dmd.114.058586. Epub 2014/07/23, PubMed PMID: 25048520.
Hartmann, E.K., Ziebart, A., Thomas, R., Liu, T., Schad, A., Tews, M., et al., 2015. Inhalation therapy with the synthetic TIP-like peptide AP318 attenuates pulmonary inflammation in a porcine sepsis model. BMC Pulm. Med. 15, 7. https://doi.org/10.1186/s12890-015-0002-6. Epub 2015/04/17, PubMed PMID: 25879802; PubMed Central PMCID: PMCPMC4346123.
Hasan, M., Alam, S., Poddar, S.K., 2018. Antibody-drug conjugates: a review on the epitome of targeted anti- cancer therapy. Curr. Clin. Pharmacol. 13 (4), 236–251. https://doi.org/10.2174/1574884712666180802095521. Epub 2018/08/04, PubMed PMID: 30073930.
Hay, K.A., Hanafi, L.A., Li, D., Gust, J., Liles, W.C., Wurfel, M.M., et al., 2017. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 130 (21), 2295–2306. https://doi.org/10.1182/blood-2017-06-793141. Epub 2017/09/20, PubMed PMID: 28924019; PubMed Central PMCID: PMCPMC5701525.
Hicks, R.J., Dorow, D., Roselt, P., 2006. PET tracer development–a tale of mice and men. Canc. Imag. 6, S102–S106. https://doi.org/10.1102/1470-7330.2006. Epub 2006/11/23, 9098. PubMed PMID: 17114061; PubMed Central PMCID: PMCPMC1805077.
Hoersch, J., Hoffmann-Doerr, S., Keller, D., 2018. Derivation of an inhalation TTC for the workplace based on DNEL values reported under REACH. Toxicol. Lett. 290, 110–115.
Hutmacher, C., Neri, D., 2019. Antibody-cytokine fusion proteins: biopharmaceuticals with immunomodulatory properties for cancer therapy. Adv. Drug Deliv. Rev. 141, 67–91. https://doi.org/10.1016/j.addr.2018.09.002. Epub 2018/09/12, PubMed PMID: 30201522.
Huttunen, K.M., Raunio, H., Rautio, J., 2011. Prodrugs–from serendipity to rational design. Pharmacol. Rev. 63 (3), 750–771. https://doi.org/10.1124/pr.110.003459. Epub 2011/07/09, PubMed PMID: 21737530.
June, C.H., O'Connor, R.S., Kawalekar, O.U., Ghassemi, S., Milone, M.C., 2018. CAR T cell immunotherapy for human cancer. Science 359 (6382), 1361–1365. https://doi.org/10.1126/science.aar6711. Epub 2018/03/24, PubMed PMID: 29567707.
Kallerup, R.S., Foged, C., 2015. Classification of Vaccines. Subunit Vaccine Delivery. Springer, pp. 15–29.
Kaplon, H., Reichert, J.M., 2018. Antibodies to watch in 2018. mAbs 10 (2), 183–203. https://doi.org/10.1080/19420862.2018.1415671. Epub 2018/01/05, PubMed PMID: 29300693; PubMed Central PMCID: PMCPMC5825203.
Kapusta, D., 2007. Drug excretion. In: Enna, S.J., Bylund, D.B. (Eds.), xPharm: the Comprehensive Pharmacology Reference. Elsevier, New York, pp. 1–2.
Keedy, V., Wang, W., Schiller, J., Chada, S., Slovis, B., Coffee, K., et al., 2008. Phase I study of adenovirus p53 administered by bronchoalveolar lavage in patients with bronchioloalveolar cell lung carcinoma: ECOG 6597. J. Clin. Oncol. 26 (25), 4166–4171. https://doi.org/10.1200/JCO.2007.15.6927. Epub 2008/09/02, PubMed PMID: 18757331; PubMed Central PMCID: PMCPMC2654378.
Keitel, W.A., Atmar, R.L., 2009. Vaccines for Pandemic Influenza: Summary of Recent Clinical Trials. Vaccines for Pandemic Influenza. Springer, pp. 431–451.
Keller, B.A., Bell, J.C., 2016. Oncolytic viruses-immunotherapeutics on the rise. J. Mol. Med. (Berl.) 94 (9), 979–991. https://doi.org/10.1007/s00109-016-1453-9. Epub 2016/08/06, PubMed PMID: 27492706.
Kennedy, P.J., Oliveira, C., Granja, P.L., Sarmento, B., 2018. Monoclonal antibodies: technologies for early discovery and engineering. Crit. Rev. Biotechnol. 38 (3), 394–408. https://doi.org/10.1080/07388551.2017.1357002. Epub 2017/08/10, PubMed PMID: 28789584.
Kim, J.H., Jacob, J., 2009. DNA Vaccines against Influenza Viruses. Vaccines for Pandemic Influenza. Springer, pp. 197–210.
Kimball, K.J., Preuss, M.A., Barnes, M.N., Wang, M., Siegal, G.P., Wan, W., et al., 2010. A phase I study of a tropism-modified conditionally replicative adenovirus for recurrent malignant gynecologic diseases. Clin. Canc. Res. : Off. J. Am. Assoc. Canc. Res 16 (21), 5277–5287. https://doi.org/10.1158/1078-0432.CCR-10-0791. Epub 2010/10/28, PubMed PMID: 20978148; PubMed Central PMCID: PMCPMC2970766.
Koski, A., Bramante, S., Kipar, A., Oksanen, M., Juhila, J., Vassilev, L., et al., 2015. Biodistribution analysis of oncolytic adenoviruses in patient Autopsy samples reveals vascular transduction of noninjected tumors and tissues. Mol. Ther. 23 (10), 1641–1652. https://doi.org/10.1038/mt.2015.125. Epub 2015/07/15, PubMed PMID: 26156245; PubMed Central PMCID: PMCPMC4817914.
Krause, M.E., Sahin, E., 2019. Chemical and physical instabilities in manufacturing and storage of therapeutic proteins. Curr. Opin. Biotechnol. 60, 159–167. https://doi.org/10.1016/j.copbio.2019.01.014. Epub 2019/03/13, PubMed PMID: 30861476.
Kraynov, E., Kamath, A.V., Walles, M., Tarcsa, E., Deslandes, A., Iyer, R.A., et al., 2016. Current approaches for absorption, distribution, metabolism, and excretion characterization of antibody-drug conjugates: an industry white paper. Drug Metab. Dispos. 44 (5), 617–623. https://doi.org/10.1124/dmd.115.068049. Epub 2015/12/17, PubMed PMID: 26669328.
Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., et al., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42 (1), 65–83. https://doi.org/10.1016/j.fct.2003.08.006. Epub 2003/11/25, PubMed PMID: 14630131.
Kuehl, P.J., Boyden, T., Dobry, D.E., Doyle-Eisele, M., Friesen, D.T., McDonald, J.D., et al., 2016. Inhaled PYY(3-36) dry-powder formulation for appetite suppression. Drug Dev. Ind. Pharm. 42 (1), 150–156. https://doi.org/10.3109/03639045.2015.1036067. Epub 2015/05/27, PubMed PMID: 26006332.
Labrijn, A.F., Janmaat, M.L., Reichert, J.M., Parren, P.W., 2019. Bispecific antibodies: a mechanistic review of the pipeline. Nat. Rev. Drug Discov. 18 (8), 585–608.
Larson, C., Oronsky, B., Varner, G., Caroen, S., Burbano, E., Insel, E., et al., 2018. A practical guide to the handling and administration of personalized transcriptionally attenuated oncolytic adenoviruses (PTAVs). OncoImmunology 7 (9), e1478648. https://doi.org/10.1080/2162402X.2018.1478648. Epub 2018/09/20, PubMed PMID: 30228948; PubMed Central PMCID: PMCPMC6140583.
Le, T.T., Andreadakis, Z., Kumar, A., Roman, R.G., Tollefsen, S., Saville, M., et al., 2020. The COVID-19 vaccine development landscape. Nat. Rev. Drug Discov. 19 (5), 305–306.
Lee, D.W., Gardner, R., Porter, D.L., Louis, C.U., Ahmed, N., Jensen, M., et al., 2014. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 124 (2), 188–195. https://doi.org/10.1182/blood-2014-05-552729. Epub 2014/05/31, PubMed PMID: 24876563; PubMed Central PMCID: PMCPMC4093680.

Lenting, P.J., Denis, C.V., Christophe, O.D., 2017. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood 130 (23), 2463–2468.
Levy, G., 1994. Pharmacologic target-mediated drug disposition. Clin. Pharmacol. Ther. 56 (3), 248–252. https://doi.org/10.1038/clpt.1994.134. Epub 1994/09/01, PubMed PMID: 7924119.
Lu, J.-D., Xue, J., 2019. Chapter 101 - poisoning: kinetics to therapeutics. In: Ronco, C., Bellomo, R., Kellum, J.A., Ricci, Z. (Eds.), Critical Care Nephrology, third ed. Content Repository Only!, Philadelphia. 600-29.e7.
Machiels, J.P., Salazar, R., Rottey, S., Duran, I., Dirix, L., Geboes, K., et al., 2019. A phase 1 dose escalation study of the oncolytic adenovirus enadenotucirev, administered intravenously to patients with epithelial solid tumors (EVOLVE). J Immunother Cancer 7 (1), 20. https://doi.org/10.1186/s40425-019-0510-7. Epub 2019/01/30, PubMed PMID: 30691536; PubMed Central PMCID: PMCPMC6348630.
Mager, D.E., Jusko, W.J., 2001. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J. Pharmacokinet. Pharmacodyn. 28 (6), 507–532. https://doi.org/10.1023/a:1014414520282. Epub 2002/05/10, PubMed PMID: 11999290.
Malik, P., Phipps, C., Edginton, A., Blay, J., 2017. Pharmacokinetic considerations for antibody-drug conjugates against cancer. Pharm. Res. (N. Y.) 34 (12), 2579–2595. https://doi.org/10.1007/s11095-017-2259-3. Epub 2017/09/20, PubMed PMID: 28924691.
Mau-Sorensen, M., Dittrich, C., Dienstmann, R., Lassen, U., Buchler, W., Martinius, H., et al., 2015. A phase I trial of intravenous catumaxomab: a bispecific monoclonal antibody targeting EpCAM and the T cell coreceptor CD3. Canc. Chemother. Pharmacol. 75 (5), 1065–1073. https://doi.org/10.1007/s00280-015-2728-5. Epub 2015/03/31, PubMed PMID: 25814216.
Maus, M.V., Haas, A.R., Beatty, G.L., Albelda, S.M., Levine, B.L., Liu, X., et al., 2013. T cells expressing chimeric antigen receptors can cause anaphylaxis in humans. Cancer Immunol Res 1, 26–31. Epub 2014/01/17. PubMed PMID: 24432303; PubMed Central PMCID: PMCPMC3888798.
MedImmune. FluMist Quadrivalent [Package Insert], 2013. MedImmune, Gaithersburg, MD.
Miliotou, A.N., Papadopoulou, L.C., 2018. CAR T-cell therapy: a new era in cancer immunotherapy. Curr. Pharmaceut. Biotechnol. 19 (1), 5–18. https://doi.org/10.2174/1389201019666180418095526. Epub 2018/04/19, PubMed PMID: 29667553.
Morgan, R.A., Yang, J.C., Kitano, M., Dudley, M.E., Laurencot, C.M., Rosenberg, S.A., 2010. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol. Ther. 18 (4), 843–851. https://doi.org/10.1038/mt.2010.24. Epub 2010/02/25, PubMed PMID: 20179677; PubMed Central PMCID: PMCPMC2862534.
Moschos, S.A., Frick, M., Taylor, B., Turnpenny, P., Graves, H., Spink, K.G., et al., 2011. Uptake, efficacy, and systemic distribution of naked, inhaled short interfering RNA (siRNA) and locked nucleic acid (LNA) antisense. Mol. Ther. 19 (12), 2163–2168. https://doi.org/10.1038/mt.2011.206. Epub 2011/10/06, PubMed PMID: 21971426; PubMed Central PMCID: PMCPMC3242665.
Mueller, K.T., Maude, S.L., Porter, D.L., Frey, N., Wood, P., Han, X., et al., 2017. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. Blood 130 (21), 2317–2325. https://doi.org/10.1182/blood-2017-06-786129. Epub 2017/09/25, PubMed PMID: 28935694; PubMed Central PMCID: PMCPMC5731220.
Nations U. Globally Harmonized System of Classification and Labelling of Chemicals (GHS)2019.
Naumann, B.D., Sargent, E.V., Starkman, B.S., Fraser, W.J., Becker, G.T., Kirk, G.D., 1996. Performance-based exposure control limits for pharmaceutical active ingredients. Am. Ind. Hyg. Assoc. J. 57 (1), 33–42. https://doi.org/10.1080/15428119691015197. Epub 1996/01/01, PubMed PMID: 8588551.
Neelapu, S.S., Locke, F.L., Bartlett, N.L., Lekakis, L.J., Miklos, D.B., Jacobson, C.A., et al., 2017. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N. Engl. J. Med. 377 (26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447. Epub 2017/12/12, PubMed PMID: 29226797; PubMed Central PMCID: PMCPMC5882485.
NIOSH, 2016. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication. Number 2016-161 (Supersedes 2014-138).
NIOSH. reportTechnical Report: the NIOSH Occupational Exposure Banding Process for Chemical Risk Management. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No 2019-132. 2019.
Novartis, A., 2017. Kymriah Package Insert.
OSHA. Occupational Safety and Health Administration: Safety and Health Topics - Radiation, 2020.
Onoue, S., Aoki, Y., Matsui, T., Kojo, Y., Misaka, S., Mizumoto, T., et al., 2011. Formulation design and in vivo evaluation of dry powder inhalation system of new vasoactive intestinal peptide derivative ([R(15, 20, 21), L(17), A(24,25), des-N(28)]-VIP-GRR) in experimental asthma/COPD model rats. Int. J. Pharm. 410 (1–2), 54–60. https://doi.org/10.1016/j.ijpharm.2011.03.021. Epub 2011/03/23, PubMed PMID: 21419198.
Organization WH, 2005. WHO Biosafety Risk Assessment and Guidelines for the Production and Quality Control of Human Influenza Pandemic Vaccines, 2007.
Pfister, T., Dolan, D., Bercu, J., Gould, J., Wang, B., Bechter, R., et al., 2014a. Bioavailability of therapeutic proteins by inhalation—worker safety aspects. Ann. Occup. Hyg. 58 (7), 899–911.
Pfister, T., Dolan, D., Bercu, J., Gould, J., Wang, B., Bechter, R., et al., 2014b. Bioavailability of therapeutic proteins by inhalation–worker safety aspects. Ann. Occup. Hyg. 58 (7), 899–911. https://doi.org/10.1093/annhyg/meu038. Epub 2014/06/25, PubMed PMID: 24958792.
Phadke, A., 2008. 442. Viral pharmacokinetics and host immune response following intratumoral injection of a conditional, replicative, oncolytic adenovirus telomelysin (OBP-301). Mol. Ther. 16, S168. https://doi.org/10.1016/S1525-0016(16)39845-8.
Pinero-Lambea, C., Ruano-Gallego, D., Fernandez, L.A., 2015. Engineered bacteria as therapeutic agents. Curr. Opin. Biotechnol. 35, 94–102. https://doi.org/10.1016/j.copbio.2015.05.004. Epub 2015/06/13, PubMed PMID: 26070111.
Polu, K.R., Lowman, H.B., 2014. Probody therapeutics for targeting antibodies to diseased tissue. Expet Opin. Biol. Ther. 14 (8), 1049–1053. https://doi.org/10.1517/14712598.2014.920814. Epub 2014/05/23, PubMed PMID: 24845630.
Poon, K.A., Flagella, K., Beyer, J., Tibbitts, J., Kaur, S., Saad, O., et al., 2013. Preclinical safety profile of trastuzumab emtansine (T-DM1): mechanism of action of its cytotoxic component retained with improved tolerability. Toxicol. Appl. Pharmacol. 273 (2), 298–313. https://doi.org/10.1016/j.taap.2013.09.003. Epub 2013/09/17, PubMed PMID: 24035823.
Prudent, V., Breitbart, W.S., 2017. Chimeric antigen receptor T-cell neuropsychiatric toxicity in acute lymphoblastic leukemia. Palliat. Support Care 15 (4), 499–503. https://doi.org/10.1017/S147895151600095X. Epub 2017/01/05, PubMed PMID: 28049548; PubMed Central PMCID: PMCPMC5496800.
Rautio, J., Karkkainen, J., Sloan, K.B., 2017. Prodrugs - recent approvals and a glimpse of the pipeline. Eur. J. Pharmaceut. Sci. 109, 146–161. https://doi.org/10.1016/j.ejps.2017.08.002. Epub 2017/08/08, PubMed PMID: 28782609.
Rehman, H., Silk, A.W., Kane, M.P., Kaufman, H.L., 2016. Into the clinic: Talimogene laherparepvec (T-VEC), a first-in-class intratumoral oncolytic viral therapy. J Immunother Cancer 4, 53. https://doi.org/10.1186/s40425-016-0158-5. Epub 2016/09/24, PubMed PMID: 27660707; PubMed Central PMCID: PMCPMC5029010.
Remesh, A., 2012. Toxicities of anticancer drugs and its management. ijbcp 1. https://doi.org/10.5455/2319-2003.ijbcp000812.
Ritchie, M., Tchistiakova, L., Scott, N., 2013. Implications of receptor-mediated endocytosis and intracellular trafficking dynamics in the development of antibody drug conjugates. mAbs 5 (1), 13–21. https://doi.org/10.4161/mabs.22854. Epub 2012/12/12, PubMed PMID: 23221464; PubMed Central PMCID: PMCPMC3564878.
Roberts, S.A., Andrews, P.A., Blanset, D., Flagella, K.M., Gorovits, B., Lynch, C.M., et al., 2013. Considerations for the nonclinical safety evaluation of antibody drug conjugates for oncology. Regul. Toxicol. Pharmacol. 67 (3), 382–391. https://doi.org/10.1016/j.yrtph.2013.08.017. Epub 2013/09/10, PubMed PMID: 24012707.
Rosewell Shaw, A., Suzuki, M., 2016. Recent advances in oncolytic adenovirus therapies for cancer. Curr. Opin. Virol 21, 9–15. https://doi.org/10.1016/j.coviro.2016.06.009. Epub 2016/07/06, PubMed PMID: 27379906; PubMed Central PMCID: PMCPMC5138135.
Russell, W.C., 2009. Adenoviruses: update on structure and function. J. Gen. Virol. 90 (Pt 1), 1–20. https://doi.org/10.1099/vir.0.003087-0. Epub 2008/12/18, PubMed PMID: 19088268.
Ryman, J.T., Meibohm, B., 2017. Pharmacokinetics of monoclonal antibodies. CPT Pharmacometrics Syst. Pharmacol. 6 (9), 576–588. https://doi.org/10.1002/psp4.12224. Epub 2017/06/28, PubMed PMID: 28653357; PubMed Central PMCID: PMCPMC5613179.
Satti, I., Meyer, J., Harris, S.A., Thomas, Z.-R.M., Griffiths, K., Antrobus, R.D., et al., 2014. Safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol in BCG-vaccinated healthy adults: a phase 1, double-blind, randomised controlled trial. Lancet Infect. Dis. 14 (10), 939–946.
Schmidt-Wolf, I.G., Negrin, R.S., Kiem, H.P., Blume, K.G., Weissman, I.L., 1991. Use of a SCID mouse/human lymphoma model to evaluate cytokine-induced killer cells with potent antitumor cell activity. J. Exp. Med. 174 (1), 139–149. https://doi.org/10.1084/jem.174.1.139. Epub 1991/07/01, PubMed PMID: 1711560; PubMed Central PMCID: PMCPMC2118875.
Senter, P.D., 2009. Potent antibody drug conjugates for cancer therapy. Curr. Opin. Chem. Biol. 13 (3), 235–244. https://doi.org/10.1016/j.cbpa.2009.03.023. Epub 2009/05/06, PubMed PMID: 19414278.
Seth, P., Higginbotham, J., 2000. Advantages and disadvantages of multiple different methods of adenoviral vector construction. Methods Mol. Med. 45, 189–198. https://doi.org/10.1385/1-59259-079-9:189. Epub 2000/01/01, PubMed PMID: 21341057.
Sibbald, B., 2001. Death but one unintended consequence of gene-therapy trial. CMAJ (Can. Med. Assoc. J.) 164 (11), 1612. Epub 2001/06/14. PubMed PMID: 11402803; PubMed Central PMCID: PMCPMC81135.
Siddiqui, M.A.A., Perry, C.M., 2006. Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardasil®). Drugs 66 (9), 1263–1271.
Singh, G., Robinson, C.M., Dehghan, S., Jones, M.S., Dyer, D.W., Seto, D., et al., 2013. Homologous recombination in E3 genes of human adenovirus species D. J. Virol. 87 (22), 12481–12488. https://doi.org/10.1128/JVI.01927-13. Epub 2013/09/13, PubMed PMID: 24027303; PubMed Central PMCID: PMCPMC3807923.
Singh, S., Kumar, N.K., Dwiwedi, P., Charan, J., Kaur, R., Sidhu, P., et al., 2018. Monoclonal antibodies: a review. Curr. Clin. Pharmacol. 13 (2), 85–99. https://doi.org/10.2174/1574884712666170809124728. Epub 2017/08/12, PubMed PMID: 28799485.
Stanard, B., Dolan, D.G., Hanneman, W., Legare, M., Bercu, J.P., 2015. Threshold of toxicological concern (TTC) for developmental and reproductive toxicity of anticancer compounds. Regul. Toxicol. Pharmacol. 72 (3), 602–609.
Stanford. Stanford Environmental Health and Safety: Adenovirus Fact Sheet, 2020.

Stein, C.A., Castanotto, D., 2017. FDA-approved oligonucleotide therapies in 2017. Mol. Ther. 25 (5), 1069–1075.

Strohl, W.R., 2015. Fusion proteins for half-life extension of biologics as a strategy to make biobetters. BioDrugs 29 (4), 215–239. https://doi.org/10.1007/s40259-015-0133-6. Epub 2015/07/17, PubMed PMID: 26177629; PubMed Central PMCID: PMCPMC4562006.

Taft, D.R., 2009. Chapter 9 - drug excretion. In: Hacker, M., Messer, W., Bachmann, K. (Eds.), Pharmacology. Academic Press, San Diego, pp. 175–199.

Tarhini, A., Lo, E., Minor, D.R., 2010. Releasing the brake on the immune system: ipilimumab in melanoma and other tumors. Cancer Biother. Radiopharm. 25 (6), 601–613. https://doi.org/10.1089/cbr.2010.0865. Epub 2011/01/06, PubMed PMID: 21204754; PubMed Central PMCID: PMCPMC3011989.

Templin, M.V., Levin, A.A., Graham, M.J., Aberg, P.M., Axelsson, B.I., Butler, M., et al., 2000. Pharmacokinetic and toxicity profile of a phosphorothioate oligonucleotide following inhalation delivery to lung in mice. Antisense Nucleic Acid Drug Dev. 10 (5), 359–368. https://doi.org/10.1089/oli.1.2000.10.359. Epub 2000/11/18, PubMed PMID: 11079575.

Tian, G., Liu, J., Zhou, J.S., Chen, W., 2009. Multiple hepatic arterial injections of recombinant adenovirus p53 and 5-fluorouracil after transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a pilot phase II trial. Anti Canc. Drugs 20 (5), 389–395. https://doi.org/10.1097/CAD.0b013e32832a2df9. Epub 2009/03/17, PubMed PMID: 19287305.

Trivedi, A., Stienen, S., Zhu, M., Li, H., Yuraszeck, T., Gibbs, J., et al., 2017. Clinical pharmacology and translational aspects of bispecific antibodies. Clin. Transl. Sci. 10 (3), 147–162. https://doi.org/10.1111/cts.12459. Epub 2017/03/16, PubMed PMID: 28297195; PubMed Central PMCID: PMCPMC5421745.

van Schalkwyk, M.C., Papa, S.E., Jeannon, J.P., Guerrero Urbano, T., Spicer, J.F., Maher, J., 2013. Design of a phase I clinical trial to evaluate intratumoral delivery of ErbB-targeted chimeric antigen receptor T-cells in locally advanced or recurrent head and neck cancer. Hum Gene Ther. Clin. Dev. 24 (3), 134–142. https://doi.org/10.1089/humc.2013.144. Epub 2013/10/09, PubMed PMID: 24099518.

Vande Casteele, N., Gils, A., 2015. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: adding value to current practice. J. Clin. Pharmacol. 55 (S3), S39–S50.

Vasquez, K.M., Narayanan, L., Glazer, P.M., 2000. Specific mutations induced by triplex-forming oligonucleotides in mice. Science 290 (5491), 530–533.

Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W., Kopple, K.D., 2002. Molecular properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 45 (12), 2615–2623. https://doi.org/10.1021/jm020017n. Epub 2002/05/31, PubMed PMID: 12036371.

Vormittag, P., Gunn, R., Ghorashian, S., Veraitch, F.S., 2018. A guide to manufacturing CAR T cell therapies. Curr. Opin. Biotechnol. 53, 164–181. https://doi.org/10.1016/j.copbio.2018.01.025. Epub 2018/02/21, PubMed PMID: 29462761.

Walker, M.P., Cowlen, M., Christensen, D., Miyamoto, M., Barley, P., Crowder, T., 2017. Nonclinical safety assessment of SPX-101, a novel peptide promoter of epithelial sodium channel internalization for the treatment of cystic fibrosis. Inhal. Toxicol. 29 (8), 356–365. https://doi.org/10.1080/08958378.2017.1366602. Epub 2017/10/07, PubMed PMID: 28984146.

Wang, Z., 2017. Clinical pharmacological considerations on CAR-T cell therapy for cancer. J. Pharmacol. Clin. Res. 3 https://doi.org/10.19080/JPCR.2017.03.555619.

Wechman, S.L., Rao, X.M., McMasters, K.M., Zhou, H.S., 2016. Adenovirus with DNA packaging gene mutations increased. Virus Release. Viruses. 8 (12) https://doi.org/10.3390/v8120333. Epub 2016/12/22, PubMed PMID: 27999391; PubMed Central PMCID: PMCPMC5192394.

WHO, 2019. WHO Recommendations for Routine Immunization Summary Tables [cited 2020 August 7]. Available from: https://www.who.int/immunization/policy/immunization_tables/en/.

Wood, J.M., Robertson, J.S., 2004. From lethal virus to life-saving vaccine: developing inactivated vaccines for pandemic influenza. Nat. Rev. Microbiol. 2 (10), 842–847.

Xia, Z.J., Chang, J.H., Zhang, L., Jiang, W.Q., Guan, Z.Z., Liu, J.W., et al., 2004. [Phase III randomized clinical trial of intratumoral injection of E1B gene-deleted adenovirus (H101) combined with cisplatin-based chemotherapy in treating squamous cell cancer of head and neck or esophagus]. Ai Zheng 23 (12), 1666–1670. Epub 2004/12/17. PubMed PMID: 15601557.

Yip, A., Webster, R.M., 2018. The market for chimeric antigen receptor T cell therapies. Nat. Rev. Drug Discov. 17 (3), 161–162. https://doi.org/10.1038/nrd.2017.266. Epub 2018/01/30, PubMed PMID: 29375140.

Young, P.A., Morrison, S.L., Timmerman, J.M., 2014. Antibody-cytokine fusion proteins for treatment of cancer: engineering cytokines for improved efficacy and safety. Semin. Oncol. 41 (5), 623–636. https://doi.org/10.1053/j.seminoncol.2014.08.002. Epub 2014/12/03, PubMed PMID: 25440607; PubMed Central PMCID: PMCPMC4354941.

Zalk, D.M., Nelson, D.I., 2008. History and evolution of control banding: a review. J. Occup. Environ. Hyg. 5 (5), 330–346. https://doi.org/10.1080/15459620801997916. Epub 2008/03/20, PubMed PMID: 18350442.

Zanotti-Fregonara, P., Lammertsma, A.A., Innis, R.B., 2013. Suggested pathway to assess radiation safety of (1)(8)F-labeled PET tracers for first-in-human studies. Eur. J. Nucl. Med. Mol. Imag. 40 (11), 1781–1783. https://doi.org/10.1007/s00259-013-2512-x. Epub 2013/07/23, PubMed PMID: 23868334; PubMed Central PMCID: PMCPMC3844925.