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Monoclonal Antibodies Handling and Administration Risk Management

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ABSTRACT

Background

The use of Monoclonal Antibodies (MABs) has provided a new approach to treat various diseases and is in constant evolution. Hospital at home, new regulations and technologies are the next challenges for which healthcare professionals are confronted with. Therefore, risk assessment of MAB handling and administration must be considered.

The aim of this study was to develop a tool providing recommendations regarding the MAB handling and administration.

Method

A review of the scientific literature was undertaken to identify MABs hazard characteristics, their immunogenic potential and their complexity of preparation. A tool was developed to classify MABs requiring a preparation in different groups providing specific handling and administration recommendations.

Results

An evaluation algorithm was developed to classify MABs regarding their toxicity and complexity of preparation.

28 MABs and 2 fusion proteins were assessed: 6 MABs presented a carcinogenic and/or mutagenic potential in animals. More than 65% of the MABs assessed exhibited teratogenic potential and 25% were highly or moderately immunogenic.

3 groups were defined providing specific recommendations for working staff.

MAB side effects were also listed highlighting particular precautions for administration.

Conclusion

Most of the MABs assessed were not listed in known hazard drug lists (NIOSH, IARC). However, the literature reviewed has highlighted that some MABs exhibit carcinogenic or mutagenic properties in animal studies. Many of them are toxic for reproduction. Furthermore, sensitizing reaction and serious side effects can be observed.

Despite their high molecular weight, MABs inhalation (ability to generate aerosol or powder handling) has been described as a potential route of occupational exposure.

Studies on humans at low dose exposure should be conducted to allow the establishment of clear safety guidance for MABs handling and administration.

Keywords: Monoclonal antibodies, Handling risk, Occupational exposure, Health quality, Patient safety, Chemotherapy.

INTRODUTION

Monoclonal antibodies (MABs) are now part of the therapeutic arsenal used by the healthcare professional to

treat several diseases such as malignancies, transplant rejection, autoimmune and infectious diseases. The number of MABs available on the market has substantially increased and many are still under investigation.

The expected arrival of avelumab, atezolizumab, blimatumomab, durvalumab or dinutuximab is examples illustrating the expansion of MABs used in immunotherapy.

According to the National Institute for Occupational Safety and Health (NIOSH), a hazardous drug is defined as a substance exhibiting carcinogenicity, teratogenicity, developmental or reproductive toxicity, genotoxicity or organ toxicity at low dose [1].

For a long period MABs were considered as hazardous drugs. However, due to their specific targeted mechanisms of action and their high molecular weight, MABs were re-evaluated by the NIOSH and were removed from the NIOSH list [2]. In the last published NIOSH list (2016), the only non-conjugate MABs was the pertuzumab.

MABs do not always fulfill conventional hazardous drug criteria and information available does not permit to assign an appropriate hazard classification [3,4].

Despite the patient quality of life improvement provided by the MAB use, severe patient side effect can be observed [5-7]. Furthermore, some MABs have a recognized toxicity and no or few long term risk of handling information is available.

Recommendations on safe handling have been published, however those do not always contain updated information, are not easily implementable, are conflicting or are specific to oncology MABS [8].

Healthcare institutions have to evolve and adapt themselves to a context where quality of care is much more important. The future arrival of new norms as PICS illustrates this.

The healthcare institutions are also confronted by new challenges as the shift of the hospital care to the home care.

In order to be integrated in these changes, MABs handling and administration risk should be assessed.

The aim of this study was to process to a review of the literature and to develop a tool assessing the MAB handling and administration risk.

METHODS

Settings

The project was conducted in a 986-bed academic hospital with an ambulatory facility. Around 3000 MABs per year are prepared in a centralized production area from the Department of Pharmacy and around 600 are prepared in the clinical area.

Literature review

From April 2016 to September 2017, a literature review was undertaken by 3 pharmacists to evaluate the chronic and acute toxicity of MABs, their immunogenic potential and their complexity of preparation. The following sources were consulted : Material Safety Data sheets (MSDS), National Institute for occupational and health list (NIOSH), International agency for research on cancer list (IARC), Summary of product characteristics (SPC), Product labeling, Food And Drug(FDA) warning box, Medline, National Health system tool and European Directive 67/548/EEC.

Different published guidelines or assessment regarding MAB handling were also taken into account [4,9,10].

This retrospective review (study) was focused on the most commonly used (and widely available in Belgium) intravenous and subcutaneous MABs. Only MABs needing a preparation before administration were included. Oral and ready to use MABs formulations were not assessed.

Abatacept and a flibercept (fusion proteins) were also integrated into the assessment.

Data analysis

Route of exposure

Routes of exposure were assessed regarding the potential contact with the drug during handling and administration (inhalation, dermal, mucosal, ocular and oral absorption).

Available guidelines and chemical properties of MABs were consulted.

Intrinsic Toxicity

The hazard of MABs was evaluated using carcinogenicity and mutagenicity data. Those toxicities were estimated based on NIOSH list, IARC list, SPC, FDA warning boxes and MSDS [1,11-21].

The same sources were used to identify the developmental toxicity/teratogenicity of MABs.

Immunogenic potential

Sensitizing properties were defined regarding the origin of MABs and were classified in 4 groups [10,12]:

1. High sensitizing potential : murine MAB (suffix momab or mumab)
2. Medium sensitizing potential : chimeric MAB (suffix ximab)
3. Low sensitizing potential : humanized MAB (suffix zumab)
4. No or negligible sensitizing potential : human MAB (suffix umab)

Complexity of preparation

The National Patient Safety Agency tool (NPSA) helps to assess the risk of injectable medicines [13].

8 risk factors were used to score the complexity of the preparation:

therapeutic risk - use of concentrate - complex calculation - complex method - reconstitution of powder in a vial - use of a part vial or ampoule or use of more than one vial or ampoule - use of a pump or syringe driver - use of non-standard giving set/device required

1. MABs with a score from 6 to 8 risk were considered as a high-risk product
2. MABs with a score from 3 to 5 risk were considered as a moderate-risk product
3. MABs with a score from 1 or 2 risk were considered as a low-risk product

Risk assessment

Different tables were created to collect and score the above information. The risk assessment tool developed by Langford & al was used for the conception of an algorithm permitting to allocate a group with specific handling and administration recommendations [10].

3 groups were defined: (Figure 1).

Group 1: MABs to be prepared in a centralized intravenous additive service (CIVARS) MABs exhibiting hazard properties (carcinogenic, mutagenic or developmental toxicity/teratogenicity) *and/or* high/medium immunogenic potential.

Group 2: MABs to be prepared in a safe environment MABs without hazard properties (carcinogenic, developmental toxicity/teratogenicity or mutagenic) and low or negligible immunogenic potential and/or moderate/high-risk factors for preparation.

Group 3: Permitted to be prepared in clinical area MABs without hazard properties (carcinogenic, developmental toxicity/teratogenicity or mutagenic) and low or negligible immunogenic potential and/o*r* low-risk factors for preparation.

MAB side effects

Specific and non-specific side effects of each MAB were reviewed and those needing particular precaution for administration were highlighted.

RESULTS

During the study period, 28 MABs were assessed. Aflibercept and abatacept were also integrated into the assessment due to their close physico-chemic properties.

Route of exposure

MABs transport, storage, preparation, administration and waste disposal are potential ways of exposure.

Dermal absorption

Given their large molecular weight (140 - 150 kDa), exposure through skin is unlikely [9]. However, local irritation, damaged skin or allergic reaction might facilitate dermal uptake [14,15].

A high incidence of dermatitis can be observed in healthcare workers, and especially nursing personnel, which can contribute to dermal uptake [16,17].

Inhalation /mucosal absorption /ocular absorption

A study was conducted using MABs (cetuximab) with a local airway delivery (via nebulization) and resulted in a promising alternative to systemic administration [18].

Despite their high molecular weight, MABs inhalation – ability to generate aerosol or powder handling – has been described as a potential route of occupational exposure [9].

Local ocular reactions are unlikely due to almost similar pH of MABs solution and lachrymal liquid [19].

Oral absorption

Although oral absorption would result in a denaturation of the MABs, systemic activity has been described in animal and

human studies. Therefore, hand to mouth contamination might be considered as a potentially viable route of internalization with unquantified effects [8,9].

Intrinsic Toxicity

No evidence of acute toxicity such as corrosive or irritant properties was highlighted [12].

Pertuzumab was the only non-conjugate MABs classified in the NIOSH hazard list published on 2016. No non conjugates MABs were founded in the IARC list 2016 [11].

Insufficient or outdated information regarding MAB toxicity were found in the safety data sheet. However, some hazard MAB properties were found in several scientific papers [20,21].

5 MABs and abatacept (+ abatacept) presented carcinogenic/mutagenic properties in animal studies.

Long term test for some MAB were conducted in animals to assess the developmental toxicity/teratogenicity. More than 65% of the MABs assessed were identified as exhibiting teratogenic activity or developmental toxicity in animals.

There is a lack of data available regarding the effect of MABs on fertility. However, studies conducted with panitumumab in female monkeys showed effect of MAB on menstrual cycle, amenorrhea or fertility [8].

The MABs toxicity data collected are summarized in Table 1.

Table 1 : Monoclonal antibodies risk assessment (hazard properties, immunogenicity, complexity of preparation)

Drug	Brand name	Target	Formulation	Molecular weight (kDa)	Carcinogenic	Mutagenic	Teratogenic /toxicity for development	Immunogenic	NHS Score [4]
Abatacept	ORENCIA®	TNFα	Powder	92	Animal studies	Animal studies	Animal studies	No or negligible	5
Abciximab	REOPRO®	GPIIb/IIIa	Solution	147	No data	No	No data	Moderate	5
Aflibercept	ZALTRAP®	VEGF	Solution	115	No data	No data	Animal studies	No or negligible	4
Alemtuzumab	LEMTRADA®	CD52	Solution	150	Yes	No data	Yes	Low	3
Belimumab	BENLYSTA®	BLyS	Powder	147	No data	No data	No data	Low	5
Bevacizumab	AVASTIN®	VEGFR	Solution	149	No data	No data	Yes	Low	3
Brentuximab vedotin	ADCETRIS®	CD30	Powder	149	No data	Animal studies	Yes	Moderate	4
Catumaxomab	REMOVAB®	CD3	Solution	151	No data	No data	No data	High	3
Cetuximab	ERBITUX®	EGFR	Solution	152	No data	No	Yes	Moderate	3
Daratumumab	DARZALEX®	CD38	Solution	148	No data	No data	No data	Low	4
Denosumab	XGEVA®	RANKL	Powder	147	No data	No data	Yes	Low	2
Eculizumab	SOLIRIS®	C5 protein	Solution	148	No data	No data	No data	Low	2
Ibritumomab	ZEVALIN®	CD20	Solution	143	Yes	Yes	Yes	High	6
Idarucizumab	PRAXBIND®	Dabigatran	Solution	47	No data	No data	No data	Low	2
Infliximab	INFLECTRA®	TNFα	Powder	149	Yes	No	Animal studies	Moderate	5
	REMICADE®								
	REMSIMA®								
Ipilimumab	YERVOY®	CTLA-4	Solution	148	No data	No data	Animal studies	No or negligible	4
Mepolizumab	NUCALA®	IL-5	Solution	149	No data	No data	No	Low	2
Natalizumab	TYSABRI®	α4 integrin	Solution	149	No	No	Animal studies	Low	2
Nivolumab	OPDIVO®	PD-1	Solution	144	No data	No data	Yes	No or negligible	4
Obinutuzumab	GAZIVARO®	CD-20	Solution	146	No data	No data	Yes	Low	3

Palivizumab	SYNAGIS®	fusion glycoprotein of RSV	Powder	148	No data	No data	No data	Low	2
Panitumumab	VECTIBIX®	EGFR	Solution	147	No data	No data	Animal studies	No or negligible	3
Pembrolizumab	KEYTRUDA®	PD-1	Powder	149	No data	No data	Yes	Low	5
Pertuzumab	PERJETA®	HER2	Solution	148	No data	No data	Yes	Low	2
Rituximab	MABTHERA®	CD20	Solution	144	No data	No data	No data	Moderate	4
Tocilizumab	ROACTEMRA®	IL-6	Solution	145	No data	No	Animal studies	Low	4
Trastuzumab	HERCEPTINE®	HER2	Powder	148	No data	No	Yes	Low	4
Trastuzumab emtansine	KADCYLA®	HER2	Powder	>148	Animal studies	No	Yes	Low	5
Ustekinumab	STELARA®	IL-12, IL-23	Solution	148-149	No data	No data	Animal studies	No or negligible	4
Vedolizumab	ENTYVIO®	α4β7 Integrin	Powder	147	No data	No data	Animal studies	Low	3

Yes
No
No data
Animal studies

Immunogenic potential

MABs are known for their sensitizing properties. Long term exposure at low dose may lead to the formation of antibodies which may cause allergic reactions [15]. The Langford & al. classification method permitted to classify the 28 MABs in four groups. Catumaxomab and Ibritumomab showed a high immunogenic potential. 5 MABs presented a moderate risk.

The Product Characteristic Summary of the majority of the assessed MABs described infusion hypersensitivity reactions.

The immunogenic assessment is summarized in Table 1.

Complexity of preparation

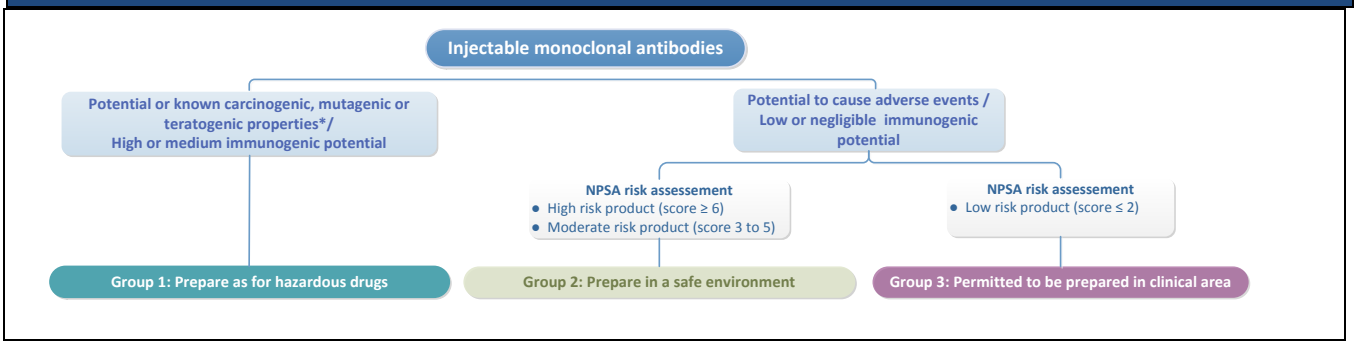
Each MAB was scored and 3 groups were identified with appropriate risk level assessment – Table 1: (NHS)

1. 6 to 8 risk factors: high-risk product, *n=7/30*
2. 3 to 5 risk factors: medium-risk product, n=22/30
3. 1 or 2 risk factors: low-risk product, n=1/30

Assessment algorithm

As described in the methodology, results collected in Table 1 were used to allocate a group for each MAB regarding the established algorithm (Figure 1).

Figure 1 : Monoclonal antibodies risk assessment algorithm



3 groups were defined with specific handling and administration recommendation Table 2.

Table 2 : Monoclonal antibodies risk classification			
Group 1 : Mab to be prepared in a centralized intravenous additive service (CIVARS)			
Abatacept	ORENCIA®	Ipilimumab	YERVOY®
Abciximab	REOPRO®	Natalizumab	TYSABRI®
Aflibercept	ZALTRAP®	Nivolumab	OPDIVO®
Alemtuzumab	LEMTRADA®	Obinutuzumab	GAZIVARO®
Bevacizumab	AVASTIN®	Panitumumab	VECTIBIX®
Brentuximab Vedotin	ADCETRIS®	Pembrolizumab	KEYTRUDA®
Catumaxomab	REMOVAB®	Pertuzumab	PERJETA®
Cetuximab	ERBITUX®	Rituximab	MABTHERA®
Denosumab	XGEVA®	Tocilizumab	ROACTEMRA®
Infliximab	INFLECTRA®	Trastuzumab	HERCEPTINE®
	REMICADE®	Trastuzumab emtansine	KADCYLA®
	REMSIMA®		
Group 2 : Mab to be prepared in a safe environment			
Belimumab	BENLYSTA®	Ustekinumab	STELARA®
Daratumumab	DARZALEX®	Vedolizumab	ENTYVIO®
Group 3 : Permitted to be prepared in clinical area			
Eculizumab	SOLIRIS®	Mepolizumab	NUCALA®
Idarucizumab	PRAXBIND®	Palivizumab	SYNAGIS®

MABs classified in group 1 were considered as hazardous requiring maximum precautions during handling and administration.

Group 2: Mab to be prepared in a safe environment *n*= 4

MABs classified in group 2 were not considered as hazardous.

Group 3: Permitted to be prepared in clinical area *n*=4

MABS classified in group 3 presented a low-risk for handling and administration.

Ibritumomab was not included in the algorithm due to be radioactive properties.

MABs side effects

Particular side effects were listed in Table 3.

Group 1: Mab to be prepared in CIVARS *n=21*

Table 3 : Monoclonal antibodies particular observation / selected side effects		
Generic Name	**Trade Name**	**Particular observation / Selected side effects**
Abatacept	ORENCIA®	Risk of infections increased / Hypersensitivity, anaphylaxis and anaphylactoid reactions / May blunt the effectiveness of some immunizations / COPD patients may develop more frequent respiratory adverse events
Abciximab	REOPRO®	Increased risk of bleeding / Intracranial hemorrhage and stroke / Hypersensitivity reaction /Thrombocytopenia
Aflibercept	ZALTRAP®	Hemorrhage / Gastrointestinal perforation / Compromised wound healing / Fistula formation / Hypertension / Proteinuria / Neutropenia and neutropenic complications / Reversible posterior leukoencephalopathy syndrome / Diarrhea and dehydratation
Alemtuzumab	LEMTRADA®	Can cause serious, sometimes fatal, autoimmune conditions as Immune thrombocytopenia antiglomerular basement membrane disease / Infusion reactions / May cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders / Thyroid disorders
Belimumab	BENLYSTA®	Mortality / Serious infections / Progressive multifocal Leukoencephalopathy / Hypersensitivity reactions / Depression / Immunization : live vaccines should not be given concurrently with Benlysta
Bevacizumab	AVASTIN®	Arterial thromboembolic events / Blood system effects / Diarrhoea and abdominal pain / Gastrointestinal perforation / Hemorrhage / Infusion reactions / Non-gastrointestinal fistula formation / Proteinuria / Revesrible posterior leukoencephalopathy syndrome / Syrgery and wound Healing complications / Can cause and/or worsen hypertension / Fatigue or asthenia

Brentuximab vedotin	ADCETRIS®	Progressive multifocal leukoencephalopathy / Peripheral neuropathy / Anaphylaxis and infusion reactions / Hematologic toxicities / Serious infections and opportunistic infections / Tumor lysis syndrome / Hepatotoxicity / Pulmonary toxicity / Serious dermatologic reactions / Gastrointestinal complication
Catumaxomab	REMOVAB®	Cytokine release related symptoms / Acute infections / Systemic Inflammatory Response Syndrome / Abdominal pain
Cetuximab	ERBITUX®	Severe infusion reactions / Cardiopulmonary arrest / Pulmonary toxicity / Electrolytic imbalance / Dermatologic toxicity (Acne-like rash was observed in the majority of clinical patients treated with Erbitux by intravenous administration) / Hypomagnesemia / Increase tumor progression, increased mortality / Ocular disorders (ulcerative keratitis)
Daratumumab	DARZALEX®	Permanently discontinue the infusion in case of life-threatening infusion reactions / Interference with cross-matching and red blood cell antibody screening / Neutropenia / Thrombocytopenia
Denosumab	XGEVA®	Osteonecrosis of the jaw / Hypocalcemia
Eculizumab	Soliris®	Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris / Discontinue Soliris in patients who are being treated for serious meningococcal infections / Use caution when administering Soliris to patients with any other systemic infection
Ibritumomab	ZEVALIN®	Serious infusion reactions / Severe Cytopenias / Severe Cutaneous and Mucocutaneous Reactions / Development of Leukemia and Myelodysplastic Syndrome / Do not administer live viral vaccines
Idarucizumab	PRAXBIND®	Thromboembolic risk / Re-elevation of coagulation parameters / Hypersensitivity reaction
Infliximab	INFLECTRA® REMICADE® REMSIMA®	Risk of serious infections / Hepatitis B virus reactivation / Hepatotoxicity : rare severe hepaticreactions / Heart failure / Cytopenia / Serieous infusion reactions / Demyelinating disease / Lupis-like syndrome / Lymphoma and other malignancies / Hepatosplenic T-cell lymphoma
Ipilimumab	YERVOY®	Immuned-mediated adverse reactions (hepatitis, endocrinopathy, dermatitis, enterocolitis, neuropathy)
Mepolizumab	NUCALA®	Hypersensitivity reactions / Do not use to treat acute bronchospasm / Herpes zoster infection / Consider varicella vaccination if appropriate before starting therapy / Decrease corticosteroids gradually upon initiation of therapy / Treat patients with pre-existing helminth infections before therapy. If patients become infected during therapy and do not respond to anti-helminth treatment discontinue Nucala® until parasitic infection resolves.
Natalizumab	TYSABRI®	Progressive multifocal leukoencephalopathy / Herpes encephalitis and meningitis / Hepatotoxicity : significant liver injury / Hypersensitivity reactions / Immunosupression / Infections
Nivolumab	OPDIVO®	Immune mediated reactions / Immune mediated pneumonitis, hepatisis, nephritis, renal dysfunction hypothyroidism and hyperthyroidism
Obinutuzumab	GAZIVARO®	Hepatisis B virus reactivation / Progressive multifocal leukoencephalopathy / Infusion reaction / Tumor lysis syndrome / Neutopenia / Thrombocytopenia / Immunization: do not administer live virus vaccines prior to or during treatment
Palivizumab	SYNAGIS®	Anaphylaxis and anaphylactic shock (including fatal cases) / Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder / Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays
Panitumumab	VECTIBIX®	Dermatologic and soft tissue toxicity / Patients with RAS-mutant mCRC : increased tumor progression, increased mortality / Infusion reactions / Electrolyte depletion / Pulmonary fibrosis/Interstitial lung disease / Ocular toxicities
Pembrolizumab	KEYTRUDA®	Immune-mediated pneumonitis, colitis, hepatisis, endocrinopathies and nephritis / Infusion-related reactions
Pertuzumab	PERJETA®	Cardiomyopathy / Left ventricular dysfonction / Infusion related reactions / Hypersensitivity reactions / Anaphylaxis
Rituximab	MABTHERA®	Fatal infusion reaction / Severe mucocutaneous reactions, some with fatal outcomes / Hepatitis B virus reactivation / Progressive multifocal leukoencephalopathy / Tumor lysis syndrome / Infections / Cardiac-arrhytmias and angina / Bowel obstruction and

		perforation / Do not administer live virrus vaccines / Cytopenias
Tocilizumab	ROACTEMRA®	Risk of serious infections / Gastrointestinal perforation / Laboratory monitoring (neutrophils, platelets, lipids and liver function) / Hypersensitivity reactions / Do not administer live vaccines
Trastuzumab	HERCEPTINE®	Cardimyopathy : Reductions in left ventricular ejection fraction / Infusion reactions / Pulmonary toxicity / Exacerbation of chemotherapy-induced Neutropenia
Trastuzumab emtansine	KADCYLA®	Hepatotoxicity / Pulmonary toxicity / Neurotoxicity / Hemorrhage / Reductions in left ventricular ejection fraction / Infusion-Related Reactions / Thrombocytopenia
Ustekinumab	STELARA®	Do not start treatment during active infection / Serious infection from mycobacteria, salmonella and BCG / Evaluate tuberculosis prior to initiating treatment / Hypersensitivity reactions / Reversible Posterior Leukoencephalopathy Syndrome / May increase risk of malignancy
Vedolizumab	ENTYVIO®	Hypersensitivity reactions / Do not administer to patients with severe infections / Progressive multifocal leukoencephalopathy

DISCUSSION

The unique specificity of each MAB does not allow considering them as a homogenous group for which general recommendations could be provided.

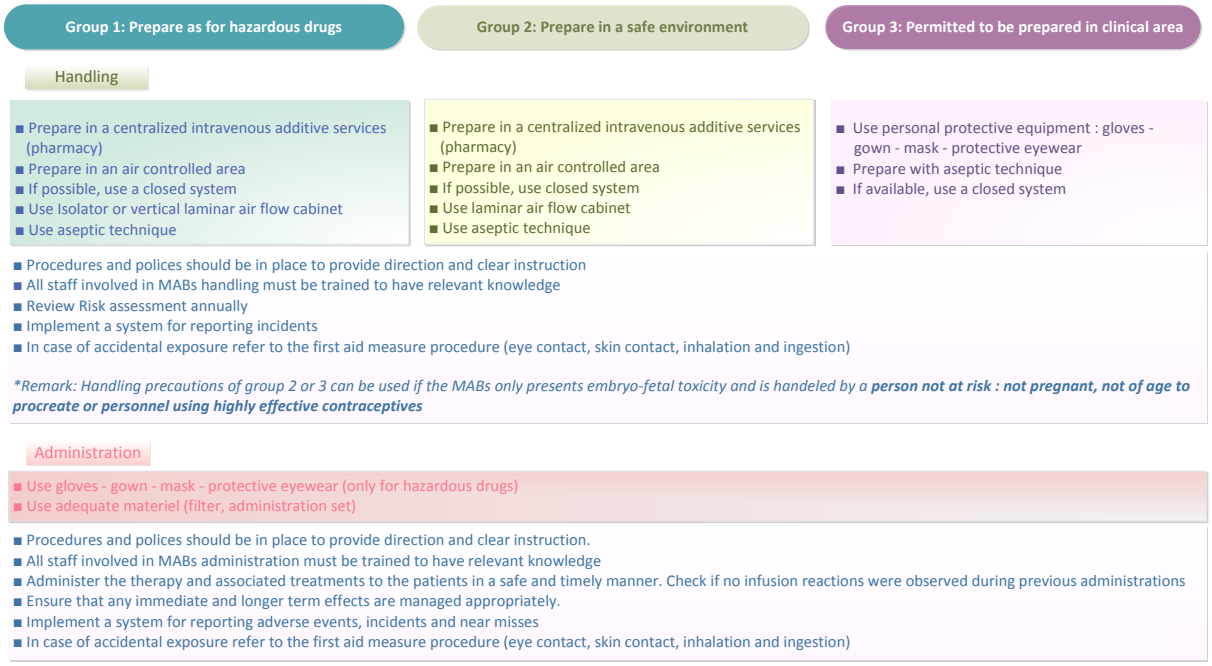
Definition of hazardous drug is not necessarily adapted for Proteinnogenic drugs and the mechanism of action of some MABs are not yet well known. Most of the MABs assessed were not listed in known hazard drug lists (NIOSH, IARC). Safety data sheets do not always permit to identify the real toxic properties of MAB, these documents are more adapted to industry practice.

Regarding the International conference (ICH) on harmonization of technical requirements for registration of pharmaceuticals for human use, carcinogenicity or genotoxicity studies are not mandatory for substances made of biotechnology [22].

FDA warning box has nevertheless highlighted the caution to take with some carcinogenic, mutagenic or developmental/teratogenic properties of some MABs [20].

Alexander *& al* realized a survey of manufacturing and handling practices for monoclonal antibodies by pharmacy, nursing and medical personnel. They concluded that MABs are most commonly handled according to cytotoxic drug standards

Figure 2 : Recommendation for MAB handling and administration



most commonly in the absence of formal guidelines. They highlighted need for guidelines for the handling of MABs [3].

The majority of MABs toxicity assessment is related to systemic doses [15]. However, Langford & al. emitted the suggestion that allergic and immunogenic reactions may not require exposure to therapeutic doses and may occur at long-term low-grade exposure [10].

MABs preparation often involves complex calculation, contamination risk, use of several /part of vial or use of non-standard material. A big part of MABs has special instructions that need to be followed during the preparation. Due to their breakable structure, the product should not be

shacked excessively.

Use of in-line filter is also currently required for MABs administration.

Those factors increase the risk of error and should be assessed for each MAB to provide adapted staff training.

Standards for safe handling of MABs are conflicting, missing, not well defined or mainly focused on MABs used in oncology.

King J & *al.* have compared different guidelines regarding the MABs handling and have highlighted variable practice recommendations [8].

Despite the limited information about occupational toxicity, the algorithm permitted to classify MABs in 3 groups.

Regarding MABs of group 1, it was important to establish safety recommendations to minimize the risk of exposure (Figure 2).

To avoid contaminations with cytotoxic-drugs, non-oncological MABs and oncological-drugs should be prepared in separated air flow cabinet. Due to the complexity of preparation of MABs included in group 2 and their potential to cause adverse events, those MABs should be prepared in a safe and centralized environment by specific trained-staff.

Pharmacy procedures should be implemented to minimize risks related to the use of personal protective equipment (gloves, mask, gown, protective eyewear) was considered as the minimum required if handling and administration of MABs are realized in clinical areas. For MABs administered outside the hospital environment (mainly subcutaneous MABs), procedures should be available to provide direction and clear instruction.

A standard operating procedure should also be available to describe the process to follow in case of spillage.

Handling precautions of group 2 or 3 could be used for MABs presenting only embryo-fetal toxicity if handled by a person not at risk (not pregnant, not of age to procreate or personnel using highly effective contraceptives) Table 4.

Table 4 : Risk assessment for staff excluding persons at risk

(not pregnant, not of age to procreate or personnel using highly effective contraceptives)

Group 1 : Mab to be prepared in a centralized intravenous additive service (CIVARS)			
Abatacept	ORENCIA®	Infliximab	INFLECTRA®
Abciximab	REOPRO®		REMICADE®
Alemtuzumab	LEMTRADA®		REMSIMA®
Brentuximab Vedotin	ADCETRIS®	Rituximab	MABTHERA®
Catumaxomab	REMOVAB®	Trastuzumab emtansine	KADCYLA®
Cetuximab	ERBITUX®		
Group 2 : Mab to be prepared in a safe environment			
Aflibercept	ZALTRAP®	Panitumumab	VECTIBIX®
Belimumab	BENLYSTA®	Pembrolizumab	KEYTRUDA®
Bevacizumab	AVASTIN®	Tocilizumab	ROACTEMRA®
Daratumumab	DARZALEX®	Trastuzumab	HERCEPTINE®
Ipilimumab	YERVOY®	Ustekinumab	STELARA®
Nivolumab	OPDIVO®	Vedolizumab	ENTYVIO®
Obinutuzumab	GAZIVARO®		

Group 3: Permitted to be prepared in clinical area			
Denosumab	XGEVA®	Natalizumab	TYSABRI®
Eculizumab	SOLIRIS®	Palivizumab	SYNAGIS®
Idarucizumab	PRAXBIND®	Pertuzumab	PERJETA®
Mepolizumab	NUCALA®		

For several MABS, toxicity data was not available. In this study, those MABs were considered as non-toxic. Therefore, MABs-related literature should be regularly reviewed to update the data basis and to adapt procedures.

Conjugated MABs to chemotherapy were all considered as toxic and placed automatically in the group 1.

MABS in clinical trials should also be assessed. In case of missing toxicity information, principle of risk minimization should be applied and should be considered as of MABs of group 1.

Patient side effects related to MAB have to be considered in order to implement safe administration procedures.

CONCLUSION

MAB interest has been demonstrated in the treatment of several diseases. Their development is constantly evolving and their field of action is expanding. Their hazard potential is nevertheless not well elucidated.

Despite the absence of MABs in the main international hazard drug list (NIOSH, IARC); some MABs exhibiting toxic potential have been identified. Data was mainly collected from animal studies Information related to MABs toxicity is very often extrapolated from systemic doses and no long-term exposures at low doses data were available.

Inhalation route has been identified as the most likely means of exposure.

Intrinsic toxicity, immunogenic potential and MAB complexity of preparation and MAB side effects should be taken into account to assess the handling and administration risks. Because insufficient data is currently available, pharmacists, technicians, nurses and physicians should proceed to a regular evaluation for safe handling and administration and to the establishment of working procedures.

Studies on human at low dose exposure should be conducted to allow the establishment of clear safety guidance for MABs handling and administration.

In case of unavailable information, principle of risk minimization should be applied.

A working group of healthcare professionals used to handle MABs should be created to establish a consensus on MABs handling and administration.

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